Chapter 6

Long-Term Outcomes of Radical Prostatectomy for Clinically Localized Prostate Adenocarcinoma

Vijaya Raj Bhatt[1], Carl M Post[2], Sumit Dahal[3], Fausto R Loberiza[4] and Jue Wang[4]*

[1]Department of Internal Medicine, Division of Hematology-Oncology, University of Nebraska Medical Center, USA
[2]College of Medicine, University of Nebraska Medical Center, USA
[3]Department of Internal Medicine, Interfaith Medical Center, USA
[4]Genitourinary Oncology Section, University of Arizona Cancer Center at St. Joseph's Hospital and Medical Center, USA

***Corresponding Author:** Jue Wang, MD, FACP, Section Leader, Genitourinary Oncology, Professor of Medicine, University of Arizona Cancer Center at Dignity Health St. Joseph's Hospital and Medical Center, 625 N. 6th St. Phoenix, AZ 85004, USA, Tel: +1 602-406-8222; Email: jue.wang@dignityhealth.org

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Abstract

Radical prostatectomy is a curative option for men with early prostate adenocarcinoma; however, many patients can have disease recurrence. The aim of this study was to determine the long-term outcomes of early prostate adenocarcinoma after radical prostatectomy. We reviewed medical records of 454 patients with clinically localized prostate adenocarcinoma, who underwent radical prostatectomy at the University of Nebraska Medical Center between 1997 and 2010. Biochemical recurrence, defined as two consecutive PSA levels of ≥ 0.2 ng/mL, was noted in 15% of patients. Only 3% of patients with biochemical recurrence died during the follow-up period, with none of the deaths attributed to prostate cancer. Our study indicates an excellent prognosis of patients with clinically localized prostate cancer following a radical prostatectomy despite a biochemical recurrence. The majority of patients with biochemical recurrence after a radical prostatectomy for clinically localized prostate cancer die from causes other than prostate cancer.

Introduction

In 2014, 233,000 new diagnoses of prostate cancer and 29,480 deaths related to prostate cancer were estimated, which highlights the public health burden of prostate cancer. The majority of prostate cancers in PSA era are localized stage at diagnosis [1]. Clinically localized prostate cancers are often treated with radical prostatectomy in patients with a life expectancy of ≥10 years (NCCN.org). A large randomized trial of 695 clinically localized prostate cancers compared the outcomes of radical prostatectomy versus watchful waiting. With a median follow-up of 23.2 years, radical prostatectomy group had lower risk of all-cause mortality (56.1% vs. 68.9%, p<.001), prostate cancer-related mortality (17.7% vs. 28.7%, p=.001) and distant metastases (26.1% vs. 38.3%, p<.001) compared to watchful waiting group. The number needed to treat to avoid one death was 8. The largest survival gain was observed in patients younger than 65 years and with intermediate risk prostate cancer [2]. This large study clearly demonstrates a benefit of radical prostatectomy, particularly in patients younger than 65 years and with intermediate risk prostate cancer. However, another large randomized trial of 731 men with localized prostate cancer failed to show any significant reduction in all-cause or prostate cancer-related mortality with radical prostatectomy as compared to observation. During a median follow-up of 10 years, all cause mortality between the groups was 47% vs. 49.9%

(p=0.22) and prostate cancer-related mortality was 5.8% vs. 8.4% (p=0.09) [3]. Outside of clinical trials, other studies have demonstrated excellent outcomes with a relatively low risk of prostate-cancer specific mortality after a radical prostatectomy [4]. Similarly, at a population-level, a study based on Surveillance, Epidemiology and End Results (SEER)-Medicare cohort demonstrated improved 10-year all-cause and prostate cancer-specific survivals with radical prostatectomy compared to watchful waiting, even after adjustment for confounding variables [5]. We reviewed our institutional data to determine the long-term outcomes of clinically localized prostate adenocarcinoma.

Materials and Methods

We conducted a retrospective analysis of all clinically localized prostate adenocarcinoma patients, who had undergone radical prostatectomy at the University of Nebraska Medical Center between 1997 and 2010. Electronic medical records were reviewed to obtain demographic information, date of diagnosis, disease characteristics at diagnosis, surgical margins, pathological staging and outcomes at last follow-up. Positive surgical margins were determined if the inked resection margin contained prostatic adenocarcinoma. Staging at the time of prostatectomy followed the AJCC 7th edition classification for genitourinary tumors. Risk level was determined using the pretreatment prostate cancer risk stratification system, which

utilizes pretreatment PSA level, biopsy Gleason Score and Tumor stage [6]. This system, initially proposed by D'Amico et al, has been validated by Mayo Clinic to be an accurate predictor of survival outcomes in patients following radical prostatectomy [7]. We determined the last follow-up, survival status and the date of death in cases of mortality using medical records and social security death index.

Following surgery, no patient received hormone or radiation therapy until biochemical recurrence was confirmed. However, patients with positive margins were permitted to undergo radiation therapy. Biochemical recurrence was defined as a rise in prostate specific antigen (PSA) to ≥0.2 ng/mL on two consecutive occasions following an undetectable PSA after initial surgery. Patients with positive surgical margin, who had detectable PSA levels following surgery but did not receive any radiation therapy were excluded. Biochemical recurrence-free survival was calculated using the date of diagnosis and the date of confirmation of elevated PSA level. Metastasis-free survival was calculated using the date of diagnosis and the date of radiological or histopathological confirmation of metastasis. Overall survival was calculated using the date of diagnosis and the date of death or last follow-up.

Survival curves were estimated at 5 and 10 years after diagnosis using the Kaplan-Meier technique. Univariate

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and multivariate analyses were conducted to calculate the risk of biochemical recurrence (treatment failure), metastasis, and overall survival. All statistical calculations were performed using SPSS 12.0 (Apache Software Foundation 2000). Results were reported as median and range values, and p-value < 0.05 was considered statistically significant. This study was approved by the University of Nebraska Institutional Review Board.

Results

A total of 454 clinically localized prostate adenocarcinoma patients, predominantly Caucasians (92%) with a median age of 60 years, underwent radical prostatectomy between 1997 and 2010 (Table 1). The majority of patients had a PSA level of ≤10 (74%), a Gleason score of ≤7 (86%), and tumor stage of ≤T2 (73%). Sixty-three percent of the patients underwent lymphadenectomy during radical prostatectomy, and the surgical margin was positive in 31% of the cases.

Table 1: Characteristics of patients with early stage prostate cancer at diagnosis

Characteristics	Total Patients, N (%)
Age at diagnosis, median (range)	60 (43-87)
Marital Status	
Married	380 (83.70)
Not married	74 (16.30)
Race	
White	420 (92.51)
Other	34 (7.49)
PSA at diagnosis, median (range)	6.1 (0.2-71.8)
PSA ≤ 4	82 (18.06)
PSA 4.1-10	257 (56.61)
PSA > 10	63 (13.88)
N/A	52 (11.45)
Gleason score at surgery	
≤ 6	131 (28.85)
= 7	260 (57.27)
≥ 8	54 (11.89)
N/A	9 (1.98)
Pathologic stage	
≤ T2	333 (73.35)
> T2	114 (25.11)
N/A	7 (1.54)
Lymphadenectomy	
Yes	290 (63.88)
No	164 (36.12)
Lymph node status	
Negative	440 (96.92)
Positive	14 (3.08)
Biochemical Recurrence	
No	388 (85.46)
Yes	66 (14.54)
Metastasis	
No	428 (94.27)
Yes	26 (5.73)
Surgical margins	
Positive	142 (31.28)
Negative	312 (68.72)

N-Number; NA-Not Available; PSA-Prostate Specific Antigen

During the median follow-up of 41 months (0.2-193 months), 14% developed biochemical recurrence with 5% developing distant metastasis. For the entire cohort, biochemical recurrence-free survival was 85% and 68% at 5 and 10 years respectively (Figure 1). Metastasis-free survival was 94% and 92% at 5 and 10 years respectively (Figure 2). Overall Survival was 94% and 80% at 5 and 10 years respectively (Figure 3). Biochemical recurrence-free survival was lower among patients with positive than negative lymph node disease (0 vs. 72% at 10 years, p<0.0001; Figure 4), positive than negative surgical margin (52% vs. 74% at 10 years, p=0.001; Figure 5) and high risk disease than either intermediate or low-risk disease (50% vs. 81% vs. 96% at 10 years, p=0.04; Figure 6).

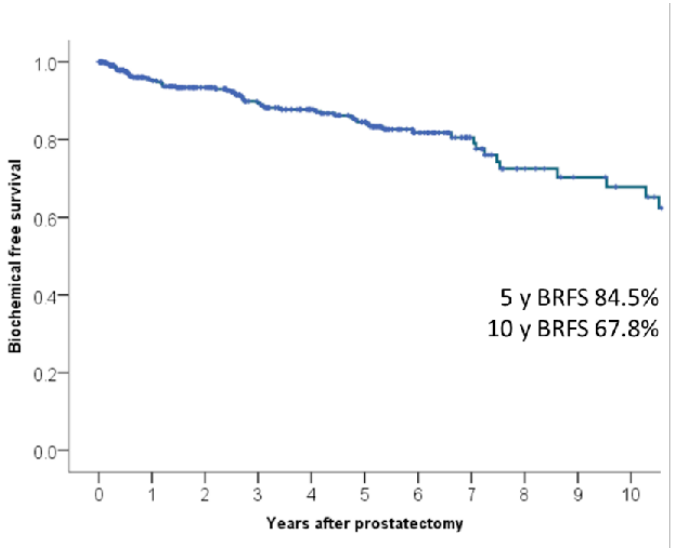

Figure 1: Biochemical recurrence-free survival for the entire cohort.

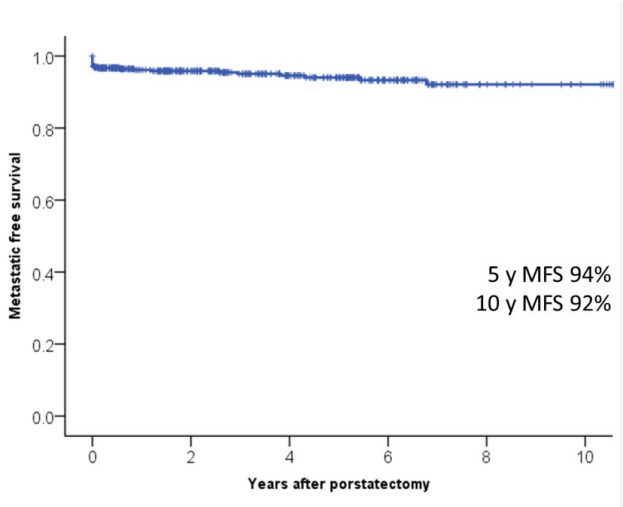

Figure 2: Metastasis-free survival for the entire cohort.

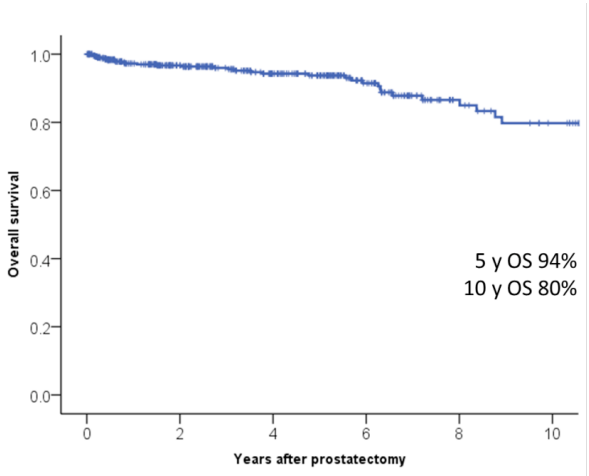

Figure 3: Overall survival for the entire cohort.

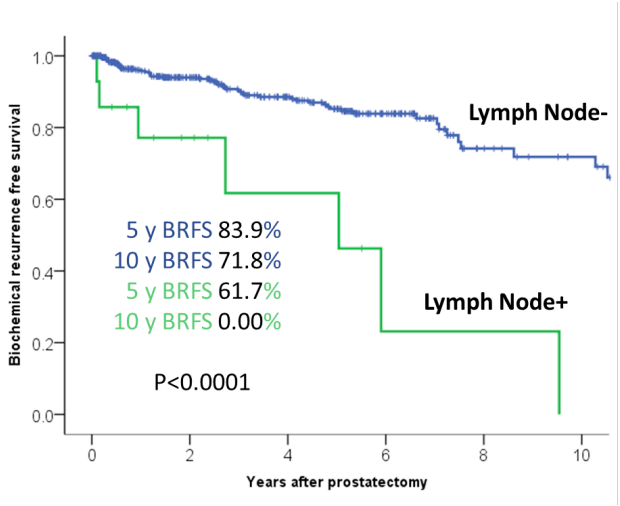

Figure 4: Biochemical recurrence-free survival based on nodal status.

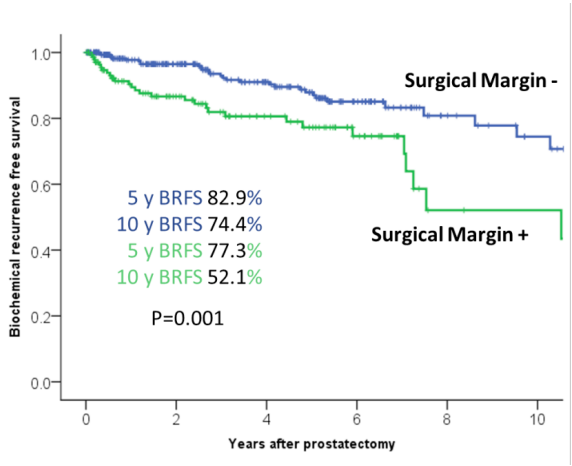

Figure 5: Biochemical recurrence-free survival based on surgical margin.

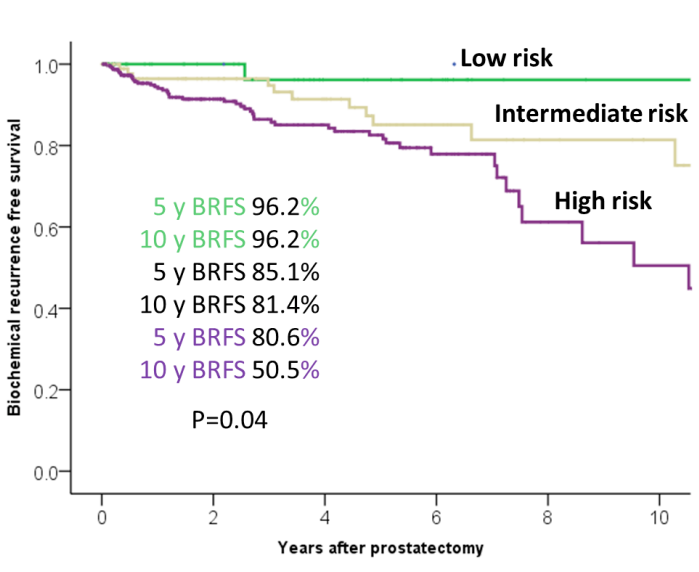

Figure 6: Biochemical recurrence-free survival based on disease risk.

A total of 32 patients died during the follow-up, with nearly three-quarter of the deaths (n=25) attributed to causes other than prostate cancer. The remaining patients (n=8) died of a cause, which could not be determined due to the presence of diverse comorbidities or the lack of medical records or follow-up. Only 2 of 66 patients with biochemical recurrence (3.0%) died during the follow-up. No deaths were attributed to prostate cancer.

In the multivariate cox regression analysis, Gleason score (hazard ratio, HR 2.41; 95% confidence interval, CI 1.13-5.15, p=0.023), positive lymph node status (HR 3.91; 95%, CI 1.48-10.29, p=0.006), and positive surgical margins (HR 1.75; 95%, CI 1.04-2.96, p=0.035) were the only factors associated with an increased risk of biochemical recurrence. Similarly, only positive lymph node status (HR 226.14; 95%, CI 42.34-1207.9, p<.0001) was associated with an increased risk of metastasis. On the other hand, factors that predicted an increased risk of mortality included surgical margins (HR 2.33; 95%, CI 1.02-5.32, p=0.044), and unknown disease status such as unknown Gleason score (HR 16.18; 95%, CI 1.70-154.2, p=0.015), pretreatment PSA level (HR 3.92; 95%, CI 1.07-14.37, p=0.040), or tumor stage (HR 0.02; 95%, CI 0.001-0.37, p=0.009).

Discussion

Our single-center study demonstrated a low risk of metastasis despite a high incidence of biochemical recurrence in patients undergoing radical prostatectomy for clinically localized prostate cancer. The majority of subsequent deaths in this population are not attributable to prostate cancer. These findings are consistent with the results of prior studies (table 2) [4,8-10]. Although the biochemical recurrence rate is as high as 30-40% at 10-15 years follow-up, the mortality from prostate cancer is 5-10% [8]. In a study from Memorial Sloan Kettering Cancer Center (n=1318), metastasis-free survival at 8 years was 97% for clinically localized prostate cancer pa-

tients following radical prostatectomy [11]. In a large Surveillance, Epidemiology and End Results registry based study, patients with localized prostate cancer (n=160787) had a 10-year cancer-specific mortality rate of 3.6% following radical prostatectomy [9]. However, an older randomized trial of patients enrolled between 1989 and 1999 with early prostate cancer showed 26% of the patients had distant metastases while 17% of them died from prostate cancer following radical prostatectomy during a median follow-up of 23 years [12]. The better outcome in modern era is likely due to stage migration from widespread adoption of PSA screening, as well as improvement in therapy of advanced disease.

Table 2: Single institution studies for radical prostatectomy.

Study	N	Median follow up (months)	PSM	BCR	Distant metastasis
Our study	454	41	31%	14%	5%
Manferrari et al. (19)	400	60	33.8%	12%	1.6%
Vrang et al. (20)	605	32	35.4%	13.4%	-
Porpiglia et al. (21)	300	62	22.7%	16%	-

BCR-Biochemical Recurrence; N-Number; PSM-Positive Surgical Margin

The overall outcome of patients with localized prostate cancer is excellent following radical prostatectomy, however, 5-10% of these patients still die of prostate cancer [8]. To predict this subset of patients at an increased risk of death, D'Amico et al demonstrated a positive relation of pretreatment PSA level, biopsy Gleason Score, and clinical tumor stage to the risk of biochemical recurrence

after radical prostatectomy [6]. Subsequently, a study from Mayo Clinic validated this classification to be an accurate predictor of the risk of biochemical and local recurrence, metastasis, and cancer-specific and overall survival after radical prostatectomy [7]. In a multicenter study, primary and secondary Gleason grade, PSA and clinical stage predicted prostate cancer-specific mortality [4]. A similar nomogram consisting of preoperative PSA, number of positive and negative biopsy cores, clinical stage, and primary and secondary Gleason grade on biopsy predicted 10-year prostate cancer recurrence (biochemical recurrence) after radical prostatectomy [13]. Another study demonstrated patients with a Gleason sum of <8 or ≤pT3a disease (favorable disease) at radical prostatectomy had improved outcomes compared to patients with a Gleason sum of 8-10 and pT3b or N1 disease (unfavorable disease). Patients with favorable disease had improved biochemical-recurrence free survival (40% vs. 4%, p<.001), metastasis-free survival (73% vs. 29%, p<.001) and prostate cancer-specific survival (84% vs. 54%, p<.001) than unfavorable disease at 10 years [14].

As a substantial proportion of patients who develop biochemical recurrence after radical prostatectomy will die of causes other than prostate cancer, there is a risk of over detection of biochemical recurrence, which increases further with increase in follow-up time interval and age of the patient at diagnosis. A recent study by Xia et al. demonstrated that almost 9% of patients with biochemical re-

currence within 5 years of radical prostatectomy are over detected and will not develop clinical metastases in the absence of salvage therapy. Similarly, almost one-third of patients over the age of 70 years at diagnosis, who developed biochemical recurrence within 10 years of surgery, were overdetected [15]. In this setting of over detection and over treatment with resulting reduction in quality of life and economic burden, newer ways of stratifying prostate cancers into lethal and indolent forms based on genomic biomarkers are being explore [16-18]. One study involving 125 prostatectomy patients identified seven regions of somatic DNA copy number alterations (CNAs) in the tumor genome to play a role in the development and progression of lethal prostate cancers. Two of these CNAs – PTEN deletion and MYC amplification- were confirmed to have significant and independent prognostic value, with 53-fold higher risk of dying for those with both these alterations in their tumor as compared to those without any [16]. Diagnostic methods that are sensitive to small amount of tumor DNA, robust to fragmented DNA, and capable of measuring all the CNAs at once, all the while being cost-effective will go a long way in providing a more accurate prognosis at the time of prostate cancer diagnosis and can be the basis for choosing between radical prostatectomy and active surveillance.

Potential limitations of this study include retrospective single center study design. Cause of deaths could

not determined in some patients because of the presence of diverse comorbidities or the lack of medical records. Despite such limitations, our study provides additional evidence that early stage prostate cancer patients have excellent outcomes after radical prostatectomy. The current definition of biochemical recurrence, however, is not a good surrogate marker for prostate cancer mortality. Not all patients with biochemical recurrence have similar prognosis, hence stratification of patients into different risk categories is essential. Studies with genomic biomarkers have shown promising results for their use as accurate prognostic markers and, ultimately, as guides to appropriate management strategy.

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References

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin. 2014; 64: 9-29.
2. Bill-Axelson A, Holmberg L, Garmo H, Rider JR, Taari K, et al. Radical Prostatectomy or Watchful Waiting in Early Prostate Cancer. N Engl J Med. 2014; 370: 932-942.

3. Wilt TJ, Brawer MK, Jones KM, Barry MJ, Aronson WJ, et al. Radical prostatectomy versus observation for localized prostate cancer. N Engl J Med. [Comparative Study Multicenter Study Randomized Controlled Trial Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. 2012; 367: 203-213.

4. Stephenson AJ, Kattan MW, Eastham JA, Bianco FJ, Vickers AJ, et al. Prostal cancer-specific mortality after radical prostatectomy for patients treated in the prostate-specific antigen era. J Clin Oncol. 2009; 27: 4300-4305.

5. Liu L, Coker AL, Du XL, Cormier JN, Ford CE, et al. Long-term survival after radical prostatectomy compared to other treatments in older men with local/regional prostate cancer. J Surg Oncol. 2008; 97: 583-591.

6. D'Amico AV, Whittington R, Malkowicz SB, Schultz D, Kaplan I, et al. Calculated prostate cancer volume greater than 4.0 cm3 identifies patients with localized prostate cancer who have a poor prognosis following radical prostatectomy or external-beam radiation therapy. J Clin Oncol. 1998; 16: 3094-3100.

7. Boorjian SA, 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: 1354-1360.

8. Boorjian SA, Eastham JA, Graefen M, Guillonneau B, Moul JW, et al. A critical analysis of the long-term impact of radical prostatectomy on cancer control and function outcomes. Eur Urol. 2012; 61: 664-675.

9. Abdollah F, Sun M, Thuret R, Jeldres C, Tian Z, et al. A competing-risks analysis of survival after alternative treatment modalities for prostate cancer patients: 1988-2006. Eur Urol. 2011; 59: 88-95.

10. Boorjian SA, Karnes RJ, Viterbo R, Rangel LJ, Bergstralh EJ, et al. Long-term survival after radical prostatectomy versus external-beam radiotherapy for patients with high-risk prostate cancer. Cancer.

11. Zelefsky MJ, Eastham JA, Cronin AM, Fuks Z, Zhang Z, 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: 1508-1513.

12. Bill-Axelson A, Holmberg L, Garmo H, Rider JR, Taari K, et al. Radical prostatectomy or watchful waiting in early prostate cancer. N Engl J Med. 2014; 370: 932-942.

Recent Advances in Prostate Cancer

13. Stephenson AJ, Scardino PT, Eastham JA, Bianco FJ, Dotan ZA, et al. Preoperative nomogram predicting the 10-year probability of prostate cancer recurrence after radical prostatectomy. J Natl Cancer Inst. 2006; 98: 715-717.

14. Pierorazio PM, Ross AE, Lin BM, Epstein JI, Han M, et al. Preoperative characteristics of high-Gleason disease predictive of favourable pathological and clinical outcomes at radical prostatectomy. BJU Int. 2012; 110: 1122-1128.

15. Xia J, Trock BJ, Gulati R, Mallinger L, Cooperberg MR, et al. Overdetection of recurrence after radical prostatectomy: estimates based on patient and tumor characteristics. Clin Cancer Res. 2014; 20: 5302-5310.

16. Liu W, Xie CC, Thomas CY, Kim ST, Lindberg J, et al. Genetic markers associated with early cancer-specific mortality following prostatectomy. Cancer. [Research Support, N.I.H., Extramural Research Support, U.S. Gov't, Non-P.H.S.]. 2013; 119 : 2405-2412.

17. Karnes RJ, Bergstralh EJ, Davicioni E, Ghadessi M, Buerki C, et al. Validation of a Genomic Classifier that Predicts Metastasis Following Radical Prostatectomy in an At Risk Patient Population. The Journal of Urology. 2013; 190: 2047-2053.

18. Cooperberg M, Simko J, Falzarano S, Maddala T, Chan J, et al. Development and validation of the biopsy-based genomic prostate score (GPS) as a predictor of high grade or extracapsular prostate cancer to improve patient selection for active surveillance. J Urol. 2013; 189: 873.

19. Manferrari F, Brunocilla E, Baccos A, Bertaccini A, Garofalo M, et al. Laparoscopic radical prostatectomy: 10 years of experience at a single institution. Anticancer Res. 2014; 34: 2443-2448.

20. Vrang ML, Roder MA, Vainer B, Christensen IJ, Gruschy L, et al. First Danish single-institution experience with radical prostatectomy: impact of surgical margins on biochemical outcome. Scand J Urol Nephrol. 2012; 46: 172-179.

21. Porpiglia F, Fiori C, Manfredi M, Grande S, Poggio M, et al. Surgical margin status of specimen and oncological outcomes after laparoscopic radical prostatectomy: experience after 400 procedures. World J Urol. 2012; 30: 245-250.