TURKISH JOURNAL OF UROLOGY Turk J Urol 2017; 43(1): 36-41 • DOI: 10.5152/tud.2016.09476

UROONCOLOGY

Original Article

Robot-assisted radical prostatectomy in low- and high-risk prostate cancer patients

Düşük ve yüksek riskli prostat kanseri hastalarında robot-yardımlı radikal prostatektomi

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ABSTRACT

Objective: To evaluate the benefit of robot-assisted radical prostatectomy (RARP) in the low-risk prostate cancer (PCa) patients suitable for active surveillance and in the high-risk PCa patients who would be considered for alternative treatments such as radiotherapy (RT) and androgen deprivation therapy (ADT) instead of radical prostatectomy.

Material and methods: Of 548 patients, who underwent RARP, 298 PCa patients (258 low-risk and 40 high-risk) with a mean of 3.6 years follow-up, were included into this study. Oncological outcomes were compared separately in low- and high-risk PCa patients.

Results: The pathologic Gleason scores were ≥7 in 73 (28%), and 68 (26%) patients had a pathologic stage of T3, 29 (11%) patients had a positive surgical margin (PSM), and 20 (7%) patients had biochemical recurrence (BCR) in the first year follow-up in the low-risk group. Of 258 low-risk PCa patients, a total of 93 (36%) patients had not either BCR, pathologic Gleason score ≥7, or ≥pT3 disease with PSM. In the high-risk group, the pathologic stage was pT2 in 14 (35%) patients and 29 (72%) patients had no biochemical recurrence in the follow-up of these high-risk PCa patients. Of 40 high-risk PCa patients, in a total of 25 (62.5%) patients ≥pT3b disease, BCR, pT3a disease with PSM were not detected.

Conclusion: Approximately two thirds of high-risk PCa patients benefit from RARP without additional RT or ADT. Besides, more than one third of low-risk PCa patients who fit active surveillance criteria would have unfavorable results.

Keywords: High-risk; low-risk; prostate cancer; prostatectomy.

ÖZ

Amaç: Aktif izlem kriterlerine uygun olan düşük-riskli prostat kanseri (PCa) hastaları ile radyoterapi (RT) veya androjen deprivasyon tedavisi (ADT) gibi alternatif tedavilere uygun olan yüksek-riskli PCa hastalarında robot-yardımlı radikal prostatektomi (RYRP) tedavisinin sonuçlarını değerlendirmek.

Gereç ve yöntemler: RYRP tedavisi alan 548 PCa hastasından ortalama 3,6 yıl takip süresi olan 298 (258 düşük-risk ve 40 yüksek-risk) hasta çalışmaya dahil edildi. Onkolojik sonuçlar her bir hasta grubu için ayrı olarak değerlendirildi.

Bulgular: Düşük-riskli PCa grubunda ilk takip yılı sonunda; ≥7 patolojik Gleason skoru 73 (%28) hastada, T3 patolojik evre 68 (%26) hastada, pozitif cerrahi sınır (PCS) 29 (%11) hastada ve biyokimyasal rekürrens (BKR) 20 (%7) hastada saptandı. Düşük-riskli 258 hastanın %36'sında ≥7 patolojik Gleason skoru veya ≥pT3 veya PCS veya BKR saptandı. Yüksek-riskli PCa grubunda 14 (%35) hastanın patolojik evresi pT2 olarak gözlendi. Yüksek-riskli grubun takiplerinde 29 (%72) hastada BKR gözlenmedi. Yüksek-riskli 40 hastanın 25'inde (%62,5) BKR, PCS ile birlikte pT3a hastalık ve ≥pT3b hastalık saptanmadı.

Sonuç: Yüksek-riskli PCa hastalarının yaklaşık üçte ikisi takiplerinde RT veya ADT ihtiyacı olmadan RYRP tedavisinden fayda görmektedir. Bunun yanında, aktif izlem kriterlerine uygun olan düşük-riskli PCa hastalarının üçte birinden fazlasında beklenenden daha ileri patolojik ve klinik evre saptanabilir.

Anahtar Kelimeler: Yüksek-risk; düşük-risk; prostat kanseri; prostatektomi.

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Submitted: 09.05.2016

Accepted: 04.07.2016

Available Online Date: 06.01.2017

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Available online at www.turkishjournalofurology.com

Introduction

There are various treatment options for localized prostate cancer (PCa) including radical prostatectomy (RP), radiotherapy (RT) or active surveillance (AS). Radical prostatectomy for localized PCa increases cancer- specific survival but it has been blamed for its negative impact on quality of life.[1-3] AS has been suggested as an alternative for selected low-risk PCa patients to decrease the side effects of definitive treatment. However there is considerable variation between studies regarding the patient selection and follow-up policies for AS.[4]

Despite prostate-specific antigen (PSA) based screening for early detection of PCa, a considerable number of patients still present with high-risk features. A decade ago, there was a tendency not to operate these high-risk patients and refer them to RT and/or androgen deprivation therapy (ADT). However, not all high-risk patients have a poor prognosis after RP.[5,6] Substantial number of RP specimens of the high-risk patients reveal downgrading in the final histopathological examination when compared to preoperative biopsy results.[7]

In this study, we tried to evaluate the benefit of RP in the low-risk PCa patients suitable for AS and in the high-risk PCa patients who would be considered for alternative treatments such as RT and ADT instead of RP.

Material and methods

Patient selection

From 2008 to 2015, a total of 548 patients, aged 42-77 years (median age, 62.3 years) with localized PCa had unergone robot-assisted radical prostatectomy (RARP) in our institution. Of these, 258 were low-risk and 40 were high-risk patients with a minimum of 1-year follow-up. The local ethics committee of Ümraniye Training and Research Hospital approved this retrospective study. All patients had a minimum of ten-core biopsies, with all the biopsy specimens reviewed by the same pathologist. D'Amico's risk classification was used to define risk groups.[8] High-risk PCa was defined as PSA above 20 ng/mL or Gleason score above 7 or clinical stage of ≥T2c. Low-risk PCa was defined as PSA below 10 ng/mL, Gleason score below 7, and clinical stage of ≤cT2a.

Age, pre- and postoperative PSA, digital rectal examination findings, clinical stage and Gleason scores were prospectively collected in a database.

Surgical procedure and pathology

Robot-assisted radical prostatectomy was performed using the da Vinci Robotic System® (Intuitive Surgical, Sunnyvale, CA) by two surgeons (EG and UB) as previously reported by Gumus et al.[9] After the patient was placed in a 30-degree Trandelenburg position the surgery was performed using five trocars inserted through transperitoneal route. Following the seminal vesicle dissection, the prostate was exposed by opening the endopelvic fascia and the deep dorsal vein complex was ligated. The bladder neck was opened and the prostatic pedicles were dissected in an antegrade fashion. Bilateral nerve-sparing surgery was performed with the aid of polymer clips. The vesico-urethral anastomosis was performed using van Velthoven technique.[10] Pelvic lymphadenectomy was routinely performed on men with intermediate- or high-risk PCa. In the low-risk patients nerve-sparing technique was performed routinely.

Same pathologist in our institution reviewed both biopsy and surgical specimens. Positive surgical margin (PSM) was defined as the presence of tumor at the inked margin. Tumors with extension through the prostatic capsule were considered as pT3.

Follow-up

Demographics, preoperative, operative and all follow-up data were entered prospectively into an electronic database. The urethral catheter was removed at postoperative day 7 following a retrograde cystography. Postoperatively, all patients were followed up at 3-month intervals for the first 2 years and every 6 months for 5 years thereafter. PSA was recorded at each visit. Biochemical recurrence (BCR) was defined as two consecutive PSA values of 0.2 ng/mL or more.

Statistical analysis

Statistical analysis was performed using IBM SPSS (Statistics for Windows, Version 22.0. Armonk, NY, USA) program. Cases were divided into two groups and definitive data analysis (mean, median, range, percentages) was performed. The biochemical recurrence-free survival (BCRFS) rates were estimated using the Kaplan-Meier method and compared between low- and high-risk groups with log- rank test. A p value of <0.05 was considered as statistically significant.

Results

Table 1 shows the preoperative characteristics of the patients. Patients (total n, 548) who underwent RARP during the study period, 40 (7%) were categorized as those with high-(n=40; 7%), and low-risk PCa (258; 47%). Mean ages were similar between the high- and low-risk patients. Median follow-up was 3.6 years (min, 1 year). In the low- and high-risk groups mean pre-biopsy PSA values were 5.7 and 28.4 ng/mL, respectively.

In the low-risk group, prostate biopsy Gleason scores of the patients were ≤6 points. Low-risk patients (total n, 258) had clinical stage T1c (n= 200; 78%), and T2a (n=58; 22%)

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DOI:10.5152/tud.2016.09476

Table 1. Preoperative characteristics and comparisons between low- and high-risk patients

	Low-risk patients n=258	High-risk patients n=40
Mean age, years (range)	62.2 (42-77)	64.1 (53-73)
Mean pre-biopsy PSA value, ng/mL (range)	5.7 (3-9.8)	28.4 (3-136)
Biopsy Gleason score, n (%)		
5 or 6	258 (100)	9 (22.5)
7	-	12 (30)
8	-	16 (40)
9 or 10	-	3 (7.5)
Clinical stage, n (%)		
T1c	200 (78)	21 (52.5)
T2a	58 (22)	15 (37.5)
T2b or higher	-	4 (10)

PSA: prostate-specific antigen

Biopsy Gleason scores were ≥9 (n=3; 7.5%), 8 (n=16; 40%), 7 (n=12; 30% 9, and 6 (n=9; 22.5%) points in respective number of high-risk patients. Among 40 high-risk patients, clinical stages of T1c (n=21; 52.5%), and ≥T2a were detected. In the high-risk group 5 patients were node positive and only three of them had more than 2 positive nodes.

The results of pathologic findings and follow-up data are listed in Table 2. In the final histopathologic examination, low risk patients had Gleason score of ≥7 (n=73; 29), and pathological stage of ≥T3 (n=68; 26%). Of these low-risk patients, 29 (10%) patients had a PSM and 20 (7%) patients of them had BCR as detected during the follow-up period. Total of 10 (4%) patients in the low-risk group underwent RT and/or ADT during the follow-up period.

In the high-risk group, pathologic Gleason scores of ≥8 in 13 (24%), 7 in 20 (56%) and <7 in 7 (20%) patients were found. The pathologic stage was pT2 in 14 (35%) patients and 29 (72%) patients had no biochemical recurrence as noticed during the follow-up period of these high-risk patients. In the final pathological examination, 8 (20%) patients had PSM and 11 (28%) had BCR as found during the follow-up of these high-risk patients. In the high-risk PCa patients, the biopsy Gleason score of 8 or above were identified in 19 (47.5%) and the final pathologi-

Table 2. Postoperative results of the low- and high-risk patients

	Low-risk patients n=258	High-risk patients n=40
Pathologic Gleason score, n (%)		
5 or 6	185 (72)	7 (20)
7	69 (27)	20 (56)
8	3 (1)	7 (14)
9 or 10	1 (1)	6 (10)
Pathologic stage, n (%)		
pT2a	52 (20)	-
pT2b	3 (1)	-
pT2c	135 (52)	14 (35)
pT3a	65 (25)	20 (50)
pT3b or pT4	3 (1)	6 (15)
Positive surgical margin, n (%)	29 (11)	8 (20)
Biochemical recurrence, n (%)	20 (7)	11 (28)
Postoperative Radiotherapy, n (%)	9 (3)	6 (15)
Postoperative Hormone Therapy, n (%)	3 (1)	7 (18)

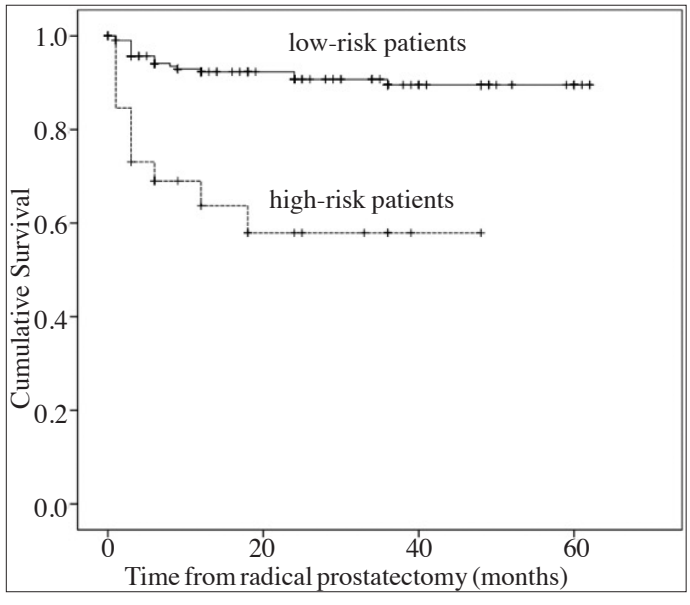

Figure 1. Kaplan-Meier analysis of biochemical recurrence- free survival rates of low- and high-risk prostate cancer patients

cal Gleason scores of ≥8 were identified in 13 (24%) patients. Totally, in 15% of these patients pathological downgrading was observed in the final pathologic examination. Postoperative RT was utilized in 6 (15%) patients and 7 (18%) patients had ADT as observed during the follow-up period.

A Kaplan-Meier analysis of BCRFS of high- and low-risk PCa patients was performed (Figure 1). The average BCRFSs were 30.2, and 56.7 months for high-, and low -risk groups, respectively (p=0.001).

Of the 258 low-risk CaP patients, a total of 93 (36%) patients have either pathologic Gleason score ≥7, or ≥pT3 disease, or have PSM or have BCR. In the high-risk group, in a total of 25 (62.5%) patients BCR, pT3a disease with PSM and ≥pT3b disease were not detected.

Discussion

Prostate cancer is the most common non-cutaneous cancer in men and approximately 14% of men will be diagnosed with PCa at some point during their lifetime.[11] PCa mostly progresses without any symptom. The presence of symptoms usually implies locally advanced or metastatic disease. RP is the first curative treatment method for PCa which is being performed for more than hundred years.[12] The SPCG-4 trial showed that, after 15 years of follow-up, RP was associated with a reduction in rates of mortality from the PCa.[2]

Over the last decade RARP was popularized mostly due to three-dimensional visualization of tissue planes and articulation capabilities. Recent literature reviews and meta-analyses showed that RARP was associated with decreased rates of PSM in low-, and intermediate risk patients, improvement in potency, recovery at short-term follow-up, and shorter hospital stay compared to open and laparoscopic RP. Also estimated blood loss and transfusion rates are reduced.[13-15] The patients with localized PCa and a life expectancy of >10 years are usually considered to benefit from RP.

With the wide use of PSA screening, the incidence of local disease has increased, whereas the incidence of metastatic disease and mortality has decreased.[16,17] The widespread use of PSA screening may cause overdiagnosis and overtreatment of the low-risk PCa.[18] However, the European Randomized Study of Screening for Prostate Cancer (ERSPC) with 13 years of follow-up confirmed a reduction in PCa mortality in men who were screened with PSA.[19] Despite the reduction in mortality, PCa treatment could have adverse effects on urinary, sexual, intestinal, and hormonal functions.[3] These results were obtained from literature of the previous decade, however recent literature reveals that these adverse effects are not as high as published before. Two meta-analysis made by Ficarra et al.[13,14] found that patients treated with RARP had continence rates of 89-100% and potency rates of 55-81% at 12 months.

Based on urinary and other adverse effects, AS was suggested to reduce the overtreatment of the selected patients with clinically organ- confined low-risk PCa. However, the selection criteria for the AS are not clear. There is a considerable variation for selection criteria among several guidelines and studies. Systematic review made by Thomsen et al.[4] concluded that selection criteria and follow-up policies vary among different studies and uncertainties persist for the long-term safety of AS. The largest cohort of AS with 993 low-risk patients and the 6.4 years follow-up showed that 27% of these patients underwent radical treatment.[20] Another problem for these AS patients is anxiety. Analysis made by Watts et al.[21] revealed that these patients have higher rates of anxiety and depression than that expected. Up to 33% of the patients who underwent RP on AS had PSMs.[22] In our study we found that 28% of the low-risk patients (Gleason score 6), were upgraded to pathologic Gleason score 7 or more. In the pathologic specimens, 11% of these patients had a PSM and 7% had a BCR within the first year of follow-up period. Overall, 36% of these low-risk patients would have unfavorable oncological outcomes if chosen for AS instead of immediate RARP.

Various urology associations and PCa study groups made different definitions for high-risk PCa. This lack of consensus on definition of high-risk PCa creates a limitation for the definition of the treatment outcomes and the designs of the study. However, Nguyen et al.[23] compared relapse-free survival rates in patients with high-risk PCa after RP determined by six different definitions and found that relapse-free survival rates after RP do not vary substantially.

Patients with high-risk PCa, have a significant risk of recurrence, disease progression, and need for the subsequent therapy. D'Amico et al.[24] found that the relative risk of PCa -specific mortality of the high-risk patients after the definitive treatment was 14.2 times higher compared with low-risk patients. However many of these cancers, which were diagnosed as high-risk are actually confined to the prostate and these patients have long-term progression-free survival after RP.[5] RT can be a favorable treatment option for the high-risk patients who do not wish to undergo surgery or those with <10 years of life expectancy. However based on the comparative data derived from the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) study it has been concluded that prostatectomy for localized PCa is associated with a significant and substantial reduction in cancer specific-mortality relative to RT and androgen-deprivation monotherapy.[25] Likewise, a meta-analysis with all published trials, which compared the outcomes of PCa patients,

Turk J Urol 2017; 43(1): 36-41
DOI:10.5152/tud.2016.09476

treated with RP or RT showed that RP have better outcomes than RT in terms of overall survival (49%) and cancer-specific mortality (44%).[26] The cohort study made by Nam et al.[27], with 15870 RP and 16595 RT patients found that patients who had undergone RT had higher incidence of secondary malignancies, and complications requiring hospital admissions, open surgical procedures, anorectal procedures. Furthermore, a recent multicentered study made by Sooriakumaran et al.[28] concluded that RP for patients with resectable distant metastasis appears safe in expert hands for meticulously selected patients. Series investigating RP in men with high-risk PCa reported PCa -specific survival rates up to 92% (72-92%) at 10 years.[29,30]

In our study, 15% of high-risk PCa patients downgraded in the final pathological examination, and 77% of the high-risk patients did not need a secondary therapy (RT or ADT) during follow-up period.

In conclusion, approximately two- thirds of high-risk PCa patients benefit from RARP without additional RT or ADT. Besides, more than one -third of low-risk PCa patients who meet active surveillance criteria would have unfavorable results.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Ümraniye Training and Research Hospital.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - A.B., U.B.; Design - A.B., U.B.; Supervision - U.B., F.F.Ö., E.G.; Resources - A.B.; Materials - A.B., E.V.K., U.B.; Data Collection and/or Processing - A.B., U.B.; Analysis and/or Interpretation - U.B., F.F.Ö., E.V.K.; Literature Search - A.B., U.B.; Writing Manuscript - A.B., U.B.; Critical Review - E.V.K., F.F.Ö., E.G.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

Etik Komite Onayı: Bu çalışma için etik komite onayı Ümraniye Eğitim ve Araştırma Hastanesi'nden alınmıştır.

Hasta Onamı: Yazılı hasta onamı bu çalışmaya katılan hastalardan alınmıştır.

Hakem Değerlendirmesi: Dış bağımsız.

Yazar Katkıları: Fikir - A.B., U.B.; Tasarım - A.B., U.B.; Denetleme - U.B., F.F.Ö., E.G.; Kaynaklar - A.B.; Malzemeler - A.B., E.V.K., U.B.; Veri Toplanması ve/veya İşlemesi - A.B., U.B.; Analiz ve/veya Yorum - U.B., F.F.Ö., E.V.K.; Literatür Taraması - A.B., U.B.; Yazıyı Yazan - A.B., U.B.; Eleştirel İnceleme - E.V.K., F.F.Ö., E.G.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

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