

## Oncologic and functional outcomes of open retropubic vs robot-assisted radical prostatectomy in patients with high risk prostate cancer

Yüksek riskli prostat kanserli hastalarda açık retropubik ve robot yardımcı radikal prostatektominin onkolojik ve fonksiyonel sonuçları

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### ÖZET

**Amaç:** Çalışmamızda yüksek riskli prostat kanserine sahip hastalarda uygulanan açık ve robot yardımcı prostatektominin onkolojik ve fonksiyonel sonuçlarının değerlendirilmesi amaçlanmıştır.

**Gereç ve Yöntemler:** Çalışmamızda deneyimli iki merkez tarafından 2014-2018 yılları arasında 118 açık radikal prostatektomi (ORP) ve 66 robot-yardımlı radikal prostatektomi (RARP) uygulanan yüksek risk prostat kanserine sahip hastaların dataları retrospektif olarak değerlendirilmiştir. D'Amico risk sınıflamasına göre prostat spesifik antijen (PSA)>20 ng/ml veya Gleason skor >7 (ISUP-grade 4/5) veya klinik evre  $\geq$  T2c componentlerinden herhangi birine sahip hastalar yüksek riskli prostat kanseri olarak kabul edilmiştir. Hastalara operasyon öncesi uzak metastazi dışlamak ve ekstrakapsüler yayılım riskini değerlendirmek amacıyla tüm abdomen manyetik rezonans görüntüleme (MRG) ve kemik sintigrafisi gerçekleştirilmiştir. Hastaların iki defa ardışık olarak değerlendirilen PSA değerinin  $\geq$  0.2 ng/mL olması biyokimyasal rekürrens olarak kabul edilmiştir. Üriner kontinans ped kullanım durumu ile erektil fonksiyon ise fosfodiesteraz tip-5 inhibitörü kullanımı ile veya kullanılmadan gerçekleştirilen vajinal penetrasyonun sözel sorgulanması ile tanımlanmıştır.

**Bulgular:** Çalışmamızda preoperatif PSA değeri, prostat biyopsi Uluslararası Ürolojik Patoloji Topluluğu (ISUP) derecesi ve klinik evre ORP grubunda istatistiksel anlamlı düzeyde daha yüksek saptanmıştır. Her iki grup arasında pozitif cerrahi sınır, ekstrakapsüler yayılım, seminal vezikül invazyonu ve lenf nod invazyonu açısından anlamlı bir fark saptanmamıştır. Biyokimyasal rekürrens ORP grubunda daha yüksek saptanmış olup androjen deprivasyon tedavisi ve radyoterapi gibi adjuvan tedaviler açısından her iki grup arasında anlamlı bir fark saptanmamıştır. Her iki grupta hastaların birinci yıl değerlendirmelerinde üriner inkontinans ve erektil disfonksiyon açısından anlamlı bir fark bulunmamıştır. Ortalama takip süresi RARP ve ORP için sırasıyla 15,55 ve 46,45 aydır.

**Sonuç:** Yüksek riskli prostat kanserinde uygulanan açık ve robot yardımcı prostatektomi onkolojik ve fonksiyonel olarak benzer sonuçlara sahiptir.

**Anahtar Kelimeler:** Radikal prostatektomi, robot-yardımlı radikal prostatektomi, yüksek riskli prostat kanseri, açık retropubik radikal prostatektomi


This study was approved by the Ethic Committee of Clinical Researches of Istanbul Medeniyet University (Approval Number: 2016/0003, Date: February 9, 2016). All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

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## ABSTRACT

**Objective:** The aim of this study is to evaluate oncological and functional outcomes of open radical prostatectomy (ORP) and robot-assisted prostatectomy (RARP) in patients with high-risk prostate cancer.

**Material and Methods:** In our study, patients with high-risk prostate cancer who underwent 118 ORP and 66 RARP between 2014-2018 have been evaluated retrospectively. Patients with prostate specific antigen (PSA) >20 ng/ml or Gleason score >7 or clinical stage  $\geq$ T2c according to D'Amico risk classifications are considered to high-risk prostate cancer. Preoperative abdominal magnetic resonance imaging (MRI) and bone scintigraphy were performed in each patient to assess the risk of extracapsular extension and exclude metastasis. The PSA value of 0.2 ng/mL in patients following two consecutive evaluations is accepted as biochemical recurrence. Urinary continence with pad use and erectile function were evaluated by verbal questioning of vaginal penetration performed with or without the use of phosphodiesterase type-5 inhibitors.

**Results:** In our study; preoperative PSA values, prostate biopsy ISUP grade, and clinical stage were found significantly higher in the ORP group. There was no significant difference between the groups in terms of positive surgical margin, extracapsular extension, seminal vesicle, and lymph node invasion. Biochemical recurrence was higher in the ORP group but there was no significant difference between the groups in terms of adjuvant treatments such as radiotherapy and androgen deprivation therapy. And there was no significant difference in urinary incontinence and erectile dysfunction in the first-year assessments of patients. Median follow-up was 15.55 and 46.45 months for RARP and ORP, respectively.

**Conclusion:** ORP and RARP have similar oncological and functional outcomes in high-risk prostate cancer.

**Keywords:** *Robot-assisted radical prostatectomy, high risk prostate cancer, open retro pubic radical prostatectomy*

## INTRODUCTION

According to 2021 data on prostate cancer by the American Cancer Society, approximately 248.000 new cases are estimated to be diagnosed in the United States, and 34.000 will die of cancer (1). Although an increase in the diagnosis of localized prostate cancer was detected with the introduction of serum prostate-specific antigen (PSA) test in clinical use, approximately 20-30% of the patients are still formed of non-metastatic high-risk prostate cancer patients (2). In the past, radical prostatectomy (RP) was recommended only for organ-confined disease due to its inadequate effect in advanced disease control and concerns about possible side effects (3). Although there are currently no randomized controlled trials that test the role of RP in high-risk patients, RP is increasingly practiced in the treatment of high-risk prostate cancer (PCA) patients and demonstrates effective oncological outcomes in the current literature (4-6). European Association of Urology (EAU) guidelines strongly recommends radical prostatectomy as a component of multi-modal therapy in patients with high-risk prostate cancer (7).

Robotic radical prostatectomy (RARP) was first described in 2001 and soon became the most preferred RP method in the United States (8). In comparative studies conducted after this rapid adaptation process, although RARP is considered as a more preferable method in functional results such as erectile function and urinary continence compared to open radical prostatectomy (ORP), the predominance of both methods is subject to discussion, especially in terms of oncological outcomes in high-risk patients (9,10).

In our study, we aimed to compare the functional and oncological outcomes of robot-assisted and open radical prostatectomy performed by two experienced centers in patients with high-risk prostate cancer.

## MATERIAL AND METHODS

Patients with high risk prostate cancer who underwent 118 open and 66 robot-assisted radical prostatectomies between 2014-2018 at two experienced centers were included in our study and patients' data were evaluated retrospectively. The surgical techniques were performed in two centers by two different urooncologists who are experienced in the field of open and robotic prostatectomy. Preoperative abdominal magnetic resonance imaging (MRI) and bone scintigraphy were performed in each patient to assess

the risk of extracapsular extension and exclude metastasis. Patients with metastatic disease at the time of admission or receiving additional treatments such as androgen deprivation therapy or radiotherapy before the operation were not included in the study. Patients whose follow-up period is less than 12 months were also not included in the study. High risk prostate cancer is defined according to the D'Amico risk classifications adopted by the current EAU guidelines. Patients with PSA > 20 ng/ml or Gleason score > 7 (ISUP grade 4/5) or clinical stage  $\geq$  T2c components were considered to have high-risk prostate cancer (7). Demographic and clinical data of patients such as age, PSA, body mass index, prostate volume, prostate biopsy result, history of prostate cancer in the family, clinical stage at the time of admission and after surgery, erectile function before operation, lymphadenectomy, final pathological stage, positive surgical margin and biochemical recurrence were recorded. The PSA value of  $\geq$  0.2 ng/mL, which was consecutively evaluated twice, was considered biochemical recurrence. Nerve-sparing surgery was performed in all patients without compromise cancer control who were potent and / or continent preoperatively and had no evidence of extracapsular disease in pre-perioperative evaluation. Extended lymph node dissection was performed in the template recommended by EAU guidelines to patients who underwent lymph node dissection (7). The potency of patients was defined as the presence of the ability to perform vaginal penetration by using with or without phosphodiesterase type 5 inhibitor. Urinary continence was evaluated by verbally questioning the use of pads and patients who do not use pads were considered continent. Complications which arose during or after the operation were evaluated and recorded according to the Clavien-Dindo complication classification (11). This study was carried out with the decision of Istanbul Medeniyet University Ethics Committee Commission dated 09.02.2016 and numbered 2016/0003.

### Statistical Analysis

Statistical Package for the Social Sciences (SPSS) program was used for statistical analysis. When evaluating study data, along with descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum), conformity of quantitative data to normal distribution was also questioned by Shapiro-Wilk test and graphical examination. Independent samples t test was used in two groups comparison of quantitative variables with normal distribution, while Mann Whitney U test was used in two group comparisons of non-normal quantitative variables. The chi-square test and Fisher's exact test were used to compare the qualitative data. Statistical significance was considered as  $p < 0.05$ .

### RESULTS

In our study, 118 ORP and 66 RARP performed for high risk prostate cancer were evaluated retrospectively. The demographic data of the patients included in the study are described in Table 1. Statistically, preoperative mean PSA, prostate biopsy ISUP and clinical stage was significantly higher in ORP group. According to the preoperative erectile function assessment, erectile dysfunction was detected in 82 of the patients in the ORP group and 13 patients in RARP group. The mean operation time was 109.2 minutes in the ORP group and 146.3 minutes in the RARP group, which was statistically significant ( $p < 0.001$ ). Statistically, perioperative mean blood loss, transfusion rate and hospitalization were significantly higher in the ORP group ( $p < 0.001$ ,  $p < 0.001$ ,  $p < 0.001$ ,  $p < 0.003$ , respectively). The mean urethral catheter duration after the operation was 14.09 days in the ORP group and 9 days in the RARP group. In our study, complications were detected in 94 patients Clavien stage-1, 23 patients stage-2 and 1 patient Clavien stage-3 in the ORP group, according to Clavien-Dindo classification, and in RARP group, Clavien stage-1 complication was detected in 66 patients ( $p < 0.001$ ).

Oncological and functional results of patients are described in Table 2. There was no significant difference between the two groups in terms of positive surgical margin, extracapsular extension (ECE), seminal vesicle invasion (SVI), lymph node invasion (LNI) and final pathological stage of radical prostatectomy. Patients with perineural invasion (PNI) were found to be statistically significantly higher in the RARP group ( $p < 0.003$ ). One hundred and eight (91.5%) patients in the ORP group and 65 (98.5%) patients in RARP

group were given extended lymph node dissection. Lymphadenectomy could not be performed for ten patients in the ORP group and one patient in the RARP group due to adhesions that developed secondary to previous abdominal or inguinal surgeries. Biochemical recurrence was statistically significant in the ORP group, while there was no significant difference between the two groups in terms of adjuvant treatments such as ADT and RT. There was no significant difference of urinary incontinence and erectile dysfunction in the first-year assessments of preoperatively potent and /or continent patients in both groups. The mean follow-up period is 46.45 months in the ORP group and 15.55 months in the RARP group ( $p < 0.001$ ).

**Table 1.** Patients' demographic and clinical features.

	Open Prostatectomy	Robot-Assisted Prostatectomy	p
Age (year)	64.7 ± 6.1	63.7 ± 5.7	0.264
PSA (ng/ml) (mean± SD, median)	31.38 ± 29.6, 23	21.08 ± 19.82, 15.5	0.013
Body Mass Index (kg/m <sup>2</sup> )	26.8 ± 8.3	26.4 ± 2.6	0.435
Prostate Volume (mm <sup>3</sup> )	44.6 ± 20.03	49.06 ± 28.8	0.220
TRUS biopsy ISUP Grade Group			0.001
1	19 (16.1%)	6 (9.1%)	
2	9 (7.6%)	16 (24.2%)	
3	25 (21.2%)	11 (16.7%)	
4	40 (33.9%)	29 (43.9%)	
5	25 (21.2%)	4 (6.1%)	
Family History (Prostate Cancer)	15 (12.7%)	2 (3%)	0.034
Clinical Stage			0.001
1	30 (25.4%)	18 (27.3%)	
2	84 (71.2%)	27 (40.9%)	
3	4 (3.4%)	21 (31.8%)	
Preoperative Erectile Dysfunction	82 (69.5%)	13 (19.7%)	0.001
Operation Time (min.)	109.2 ± 18.8	146.3 ± 16.9	0.001
Mean Blood Loss (ml.)	293 ± 234	137 ± 43.2	0.001
Transfusion Rate	24 (20%)	0	0.001
Hospital Stay (day)	3.32 ± 1.7	2.65 ± 0.6	0.003
Catheter Duration (day)	14.09 ± 0.9	9 ± 1.4	0.001
Clavien-Dindo Complications			0.000
1	94 (80%)	66 (100%)	
2	23 (19.5%)		
3	1 (0.8%)		

**PSA:** Prostate Specific Antigen, **TRUS:** Transrectal Ultrasound,

**ISUP:** International Society of Urological Pathology, **SD:** Standard deviation

**Table 2.** Oncological and Functional Outcomes

	Open Prostatectomy	Robot-Assisted Prostatectomy	p
Pathological Stage			0.2
2	36 (30.5%)	18 (27.3%)	
3	78 (66.1%)	48 (72.7%)	
4	4 (3.4%)	0	
Positive Surgical Margin	42 (35.6%)	21 (31.8%)	0.631
Perineural Invasion	91 (77.1%)	62 (93.9%)	0.003
Extracapsular Extension	76 (64.4%)	43 (65.2%)	0.919
Seminal Vesicle Invasion	49 (41.5%)	29 (43.9%)	0.751
Lymph Node Invasion	11 (10.2%)	12 (18.2%)	0.165
Upgrading	47 (39.8)	18 (27.3%)	0.087
RP-ISUP Grade Group			0.005
1	10 (8.5%)	1 (1.5%)	
2	13 (11%)	9 (13.6%)	
3	15 (12.7%)	21 (31.8%)	
4	41 (34.7%)	23 (34.8%)	
5	39 (33%)	12 (18.2%)	
Biochemical Recurrence	52 (44.1%)	16 (24.2%)	0.008
Androgen Deprivation Therapy	67 (56.8%)	28 (42.4%)	0.060
Radiotherapy	66 (55.9%)	28 (42.4%)	0.078
Lymphadenectomy	108 (91.5%)	65 (98.5%)	0.056
Hormone-Resistant Prostate Cancer	11 (9.3%)	0	0.011
Mean Follow-up Time (months)	49.45 (19-210)	15.55 (12-88)	0.001
Urinary Incontinence	8 (6.8%)	6 (9.1%)	0.571
Erectile Dysfunction	20 (55.6%)	26 (49.1%)	0.547

**RP:** Radical Prostatectomy, **ISUP:** International Society of Urological Pathology,

## DISCUSSION

The high risk of disease-related metastasis and death in patients with high risk of prostate cancer has caused controversy about which treatment option can provide the best results in these patients. In this context, studies comparing radiotherapy and/or hormone therapy with RP noted that RP has better oncological and functional outcomes than other treatment methods (12-14). Although the current EAU guidelines recommends RP as a component of multi-modal treatment in high-risk patients, there is no consensus about which RP method has better oncological and/or functional outcomes (7,9,15). The limited number of comparative studies in which surgical techniques are evaluated in high-risk patients in current literature is one of the most important reasons for the lack of knowledge on this subject. Another important point is the involvement of more than one surgeon in the study group and exchange of experience of multiple surgeons (16). Achieving the negative surgical margin during radical prostatectomy in patients with high-risk prostate cancer is both difficult and requires a high level of technical expertise. In the studies conducted by experienced surgeons, they stated that the surgery performed in patients with high-risk prostate cancer does not cause an increase in morbidity compared to the low-risk group and surgical experience has an important place in patients with high-risk prostate cancer (17,18). In this regard, the RP results

of two surgeons who are highly experienced in oncological surgeries, especially in prostate cancer, were compared. Both surgeons had surgical experience, having completed the learning curve in ORP and RARP.

Based on the results of ORP and RARP performed to high-risk prostate cancer patients in the literature, surgical margin positivity, biochemical recurrence and biochemical recurrence-free survival is similar in terms of the necessity of additional treatment after surgery and oncological consequences (9,10,12,16,19). In a retrospective study by Harty et al. in which they evaluated 153 ORP and 152 RARP patients with high risk prostate cancer, the positive surgical margin was 52.9% and 50% respectively and it was noted that there is no significant difference between the two groups (16). In the study of Pierorazio et al., 743 ORP and 105 RARP patients were evaluated and the positive surgical margin rates were found to be 29.4% and 27.7% (12). In our study, positive surgical margin rates were 35.6% and 31.8% respectively in ORP and RARP groups, and there was no significant difference between the two groups. This ratio is higher than that of Pierorazio's study. The high percentage of  $\geq$ pT3 patients (69.5% and 72.7% respectively) in both ORP and RARP groups may be a reason for high surgical margin rates.

Positive surgical margin findings detected during prostatectomy or pathological examination in conducted studies are stated to be associated with poor prognosis and is an independent risk factor for biochemical recurrence (20). No significant relationship was found between surgical technique and biochemical recurrence risk in a multivariate analysis of the study by Shapiro et al. in which 337 patients who were conducted ORP and RARP and showed positive surgical margin were evaluated (21). Again, based on a multivariate analysis of a study where ORP and RARP values of intermediate and high-risk patients were evaluated, Gleason score, extraprostatic extension, positive surgical margin and lymph node involvement is stated to be independent determiners for biochemical recurrence, but there is no difference between surgical methods in terms of biochemical recurrence (22). In the study of Lee et al. evaluated 356 high-risk prostate cancer patients with pT3 stage and above, Gleason 8-10 or PSA value of 20 ng / ml; stated that clinical T stage, pathological T stage and pathological Gleason score were independent predictive factors for biochemical recurrence, while ORP and RARP surgical techniques were not associated with positive surgical margins and biochemical recurrence (23). In our study, there was no difference between the two surgical techniques in terms of pathological stage, positive surgical margin, extracapsular extension, seminal vesicle invasion and lymph node involvement. Although there was no significant difference between groups in view of the pathological findings that have an important role in the course of the disease, biochemical recurrence rate was higher in the ORP group. Although recurrence rate was higher in the ORP group, there was no significant difference between the two groups in terms of post-surgical treatment modalities. Primarily, the fact that most of the patients in the ORP group consisted of patients with ISUP grade 4-5 may have caused the biochemical recurrence to be higher in the ORP group. In addition, the longer follow-up time in the ORP group when compared to the RARP group can be considered another reason.

Some of the known advantages of minimally invasive surgery in comparison with ORP are rapid recovery, less bleeding and reduced use of analgesics. The meta-analysis conducted by Tawari et al. to compare ORP and RARP, showed more than 7% risk of perioperative complications for ORP in all risk groups and two times more hospital stay (3). In comparative studies on high-risk prostate cancer, Punnen et al. stated to observe significantly lower loss of blood in the RARP group in the retrospective study comparing 177 ORP and 233 RARP (10). Again, in a retrospective comparative study conducted by Gandaglia et al, it was stated that blood transfusion was lower in the RARP group when compared to the ORP group, and the hospital stay was shorter (19). The perioperative outcomes in our study are similar with the literature. Statistically, mean blood loss, transfusion rate, catheter duration and hospital stay were significantly higher in ORP group. The duration of the operation was found to be higher in the RARP group than in the ORP group. Although perioperative results appear better in RARP group, Clavien 3 complications were detected in only 1 patient and no Clavien 4-5 complications were observed in any of the patients in the ORP group. In the

RARP group, all patients were observed with Clavien-1 complication. In this regard, ORP is comparable to RARP in terms of perioperative process and complications in high-risk disease.

The most important postoperative complications of radical prostatectomy are urinary incontinence and erectile dysfunction, and higher incidence due to extensive resection applied for curative treatment in a high-risk group of patients (24). In their randomized controlled phase 3 study, Yaxley et al. assessed the oncological, functional and early postoperative results of RARP and ORP. In the study, it was stated that there was no significant difference between the surgical techniques in the early functional results and they demonstrated no difference from the updated results of this study with a longer follow up period (25, 26). Again, in a non-randomized prospective study comparing ORP and RARP by Hanglid et al., urinary incontinence rates at 12 months were respectively 20% and 21% and there was no significant difference statistically. It was also stated in the study that, when compared to ORP, RARP may have a minimal benefit in terms of erectile function (27). In the systematic review and meta-analysis of the robotic, laparoscopic, and open RP by Cao et al., there was no significant difference between the surgical methods in terms of functional outcomes between the groups (28). In the above-mentioned studies, high-risk patient population was excluded from the study while patients with a PSA value below 20 ng / ml were included in the study. In this respect, in a recent study in which Haese et al. evaluated 10,790 patients, including all risk groups, they detected higher significant continence rates in the ORP group in view of urinary incontinence at week 1 in terms of functional results, and there was no significant difference in terms of both surgical methods in the third month of patients. Considering the results of the 12th month of the study, although the continence rates were found to be higher in the RARP group, there was no significant difference between the age groups. In view of potency rates, the results show to be similar between the two groups according to the results at 12 months (29). In the current literature, there are very few functional comparative studies of surgical techniques in high-risk prostate cancer. Studies are generally based on the results of a single surgical method. Yuh et al. stated in a systematic review in which they evaluated the functional results of RARP in patients with high-risk prostate cancer, the 1-year continence rates were between 78% and 95%, and the recovery rates of erectile functions were between 52% and 60% (15). These rates are similar to studies conducted on ORP (30). According to the 1st year functional results of our study, the continence rate was 93.2% and 90.9% in the ORP and RARP group, respectively, and the potency rates were 44.4% and 50.9%, respectively, and these rates are similar to those stated in the current literature. In our study, there was no significant difference between the functional results of the two surgical techniques.

The main limitation of our study is that it is retrospective nature. Another limitation may be that preoperative characteristics are not similar between the groups. The reason for this may be that the study was conducted in two different centers and the approach in patients with high-risk prostate cancer is different. However, the absence of comparative prospective studies of surgical methods performed in patients with high-risk prostate cancer in the literature suggest that our study will be a guide for future studies on this subject.

## CONCLUSION

In our study, although ORP in patients with high risk prostate cancer has higher ISUP grade and high PSA values compared to histopathological data, it has similar oncological and functional results with RARP.

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**Conflict of interest:** The authors declare that they have no conflict of interest.

**Ethical Approval:** The study was approved by the Ethic Committee of Istanbul Medeniyet University, Goztepe Training and Research Hospital (Approval number: 2016/0003, Date: February 9, 2016). The study protocol conformed to the ethical guidelines of the Helsinki Declaration.

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