The Effect of Risk Factors on Surgical and Oncological Results in High - Risk Prostate Cancer: A Multicenter Study of the Urooncology Society, Turkey

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ABSTRACT

Purpose

To evaluate the effect of risk factors and selected surgical methods on operative and oncological results of patients undergoing radical prostatectomy (RP) with high-risk prostate cancer (HRPC).

Methods

Retrospective analysis of patients, who underwent RP for HRPC from 13 urology centers between 1990 to 2019, was performed. Groups were created according to the risk factors of D'Amico classification. Patients with one risk factor were included in group 1 where group 2 consisted of patients with two or three risk factors.

Results

A total of 1519 patients were included in this study and 1073 (70.6%) patients assigned to group 1 and 446 (29.4%) patients to group 2. Overall (biochemical and/or clinical and/or radiological) progression rate was 12.4% in group 1 and 26.5% in group 2 (p =0.001).

Surgical procedure was open RP in 844 (55.6%) patients and minimally invasive RP in 675 (44.4%) patients (laparoscopic and robot-assisted RP in 230 (15.1%) and 445 (29.3%) patients, respectively). Progression rates were similar in different types of operations (p=0.22). Progression rate was not significantly different in patients who either underwent pelvic lymph node dissection (PLND) or not in each respective group.

Conclusion

RP alone is an effective treatment in the majority of patients with HRPC and PLND did not affect the progression rates after RP. According to the number of preoperative high-risk features, as the number of risk factors increases, there is a need for additional treatment.

Keywords: Prostate cancer, radical prostatectomy, oncological results, high-risk, lymph node

What is already known about this topic?

Radical prostatectomy is a safe procedure in the treatment of prostate cancer. Prostate cancer is classified as low, medium, and high risk according to risk classifications. Treatment options are offered to patients according to their risk status. A multidisciplinary approach is applied in high-risk prostate cancer.

What does this article add?

Our study examined the operative and oncological results of patients with high-risk prostate cancer. In a multicenter study conducted with a high number of patients, it was shown that progression increased with the increase in the number of risk factors, but lymph node dissection did not affect progression.

Introduction

Prostate cancer (PC) is the second most common solid organ tumor in men. Its biological behavior varies from low-grade latent disease to high-grade progressive and metastatic aggressive tumors [1]. It is essential to distinguish aggressive forms of the disease and predict biological behavior to avoid under- or overtreatment [2]. For this purpose, different algorithms such as D'Amico risk classification and Kattan nomograms have been developed which aim to predict the pathological stage and biochemical recurrence (BCR) after radical prostatectomy (RP) [3-4]. According to the most commonly used D'Amico risk classification, prostate-specific antigen (PSA)> 20 ng / ml or Gleason score (GS)> 7 or clinical stage ≥ T2c criteria indicate high-risk disease [5]. Patients with high-risk prostate cancer (HRPC) are at higher risk for mortality, and these patients benefit from active treatment mostly in a multimodal fashion [6].

The fact that not all high-risk patients need combined therapy indicates that they do not have an equally poor prognosis [6-7]. Biochemical recurrence and cancer-specific mortality are 3.3 and 11.5 times higher in high-risk patients than in low-risk patients, respectively [8]. Although radical surgery were recommended in all major PC guidelines, NCCN guidelines specifically recommend pelvic lymph node dissection (PLND) where AUA guidelines strongly recommend surgery or androgen deprivation therapy (ADT) in combination with radiotherapy (RT) [9-11]. In this study, the effects of risk factors and selected surgical methods on surgical and oncological results of patients undergoing RP with HRPC diagnosis were investigated.

Material and Method

We retrospectively analyzed data from patients recorded in the PC Database of Urooncology Association, Turkey, between 1990 to 2019. Patients with HRPC according to D'Amico classification (≥cT2c or PSA >20 ng/ml or Gleason score >7) who underwent RP either open, laparoscopic or Robot-

assisted laparoscopic approach were included in the study cohort [9]. All procedures were performed by experienced surgeons from 13 different institutions. Exclusion criteria included a history of neoadjuvant treatment, patients with metastatic disease, incomplete pathological, and clinical data. Demographic parameters, including age, body mass index (BMI), operative data, including surgical approach, lymphadenectomy type, and complications, were recorded and analyzed.

Groups were created according to the risk factors in D'Amico classification. Patients with one risk factor were identified as favorable group (group 1) and patients with two or three risk factors are included in unfavorable group (group 2). Also, according to the applied surgical technique (open, laparoscopic, robot-assisted), patients were divided into three groups and compared. After the operation, all patients received regular follow-up every three months in the first year and every six months there after.

Endpoints of the study were:

1- Biochemical recurrence - free survival

a. Biochemical recurrence after RP was defined as PSA level above 0.2 ng/ml which was confirmed by at least two consecutive measurements

2- Progression (biochemical, clinical or radiological)-free survival (PFS) was defined as the time from the operation to the date of progression confirmed by respective methods.

3- Effect of surgical approach on oncological outcomes in patients treated with RP.

Statistical analysis

Categorical variables were expressed as numbers and percentages, whereas continuous variables were summarized as mean and standard deviation. Chi-square test was used to compare categorical variables between the groups (number of risk factors, type of operation). For comparison of groups, Oneway ANOVA was used. Regarding the homogeneity of variances, Tukey HSD or Games & Howell tests were used for multiple comparisons of groups. For univariate analysis, PFS was calculated by Kaplan-Meier method, and log-rank and Breslow tests were performed to compare PFS of the factors (number of risk factors, type of operation, age groups). All analyses were performed using IBM SPSS Statistics Version 20.0 statistical software package. The statistical level of significance for all tests was considered to be 0.05.

Results

A total of 1519 patients underwent RP due to HRPC were included in the study. The mean age of patients was 63.1 ± 6.7 years (range 40–87 years). There were 1073 (70.6%) patients in Group 1 and 446 (29.4%) patients in Group 2. Demographic and operative outcomes of these groups presented in Table 1. Minimally invasive surgical methods (laparoscopic or robot-assisted) and PLND were performed more frequently in Group 2 compared to group 1 (p=0.001, and p=0.001, respectively). PLND was performed in 53.6% of the cases in group 1 and 94.4% of group 2. Extended PLND (ePLND) was performed in 62.6% of patients in group 1 and 83.9% of patients in group 2 (p=0.001). The lymph node positivity rate was 10.1% and 28% in Groups 1 and 2, respectively (p=0.001).

The mean follow-up duration was 43±1.2 months and 31.7±2.1 months for Group 1 and 2, respectively (p=0.001). The mean PFS was 151.9 months (95% CI: 143.5-160.4). PFS was significantly longer in Group 1 (161.4 months (95% CI: 151.3-171.5)) compared to Group 2 (94 months (95% CI: 85.0-108.0)) (p =0.001) (Fig.1). The mean PFS was 156.1 months (95% CI: 140.8-171.5), 148.8 months (95% CI: 137.7-159.9) and 142.9 months (95% CI: 125.0-160.9) for the age groups of 40-59 years, 60-69 years and over 70 years, respectively. The mean PFS duration decreased with increasing age (p = 0.017). Total progression rate defined as biochemical, clinical and radiological progression was 12.4% in group 1 and 26.5% in group 2 (p =0.001). The number of risk factors was associated with adverse pathological outcomes (Table 2).

Overall, progression rate was significantly higher in patients with PLND [185 (19.1%)], compared to patients without PLND [66 (12.8%)] (p=0.002). However, analysis of each group in itself did not reveal any significant difference, Progression was observed, in 75 (13.2%) and 58 (11.8%) patients with or without PLND in group 1(p =0.46). In group 2, progression was seen in 110 (27.3%) patients with PLND and 8 (32%) patients without PLND (p = 0.61). Thus, PLND did not affect the progression rates after RP in each group. There was a statistically significant difference in terms of progression between those with and without lymph node positivity (42.7% vs 15.4%, p=0.001).

Per-Operative Outcomes

Open RP was performed in 844 (55.6%) patients, 230 (15.1%) patients underwent laparoscopic RP, and 445 (29.3%) patients underwent robot-assisted RP. The mean operation time in open, laparoscopic, and robot-assisted RP was 157.7, 198.0, and 240.5 minutes respectively (p=0.001). The average blood loss in these operations was 537, 262.7, and 211.9 ml, respectively] (p=0.001).

PLND and ePLND were performed significantly more frequently in patients who underwent robot-assisted and laparoscopic RP compared to open RP (p=0.001) (Table 3). Progression rates were similar in different types of operations (p=0.22). Progression and pathological data of the patients according to the type of operation are summarized in Table 4.

Neoadjuvant treatment was administered to 61 (4%) patients, while 384 (25.3%) patients received adjuvant treatment and 1135 (74.7%) did not require any additional therapy. The need for additional postoperative treatment such as ADT and/or RT, was significantly higher in Group 2 than in Group 1 (43.9% vs. 17.5%, respectively; p=0.001). The progression rate was significantly high in patients treated with any additional treatment (54.4% vs 3.7%, p=0.001). Neoadjuvant and adjuvant treatments according to risk factors, are shown in Table 5.

Discussion

The majority of men with low- or intermediate-risk PC are effectively managed with active surveillance, surgery, radiation or even watchful waiting. It is important to identify men with high-risk disease because it is associated with a significant mortality thus critical for management planning. Herein, by using the PC Database of the Urooncology Association, Turkey, it has been shown that open or minimally invasive RP alone is an effective treatment in patients with HRPC. It was found that the probability of progression increased as the number of risk factors increased, and the need for additional treatment such as ADT and/or RT was higher in the peri-operative period.

There is still no consensus about the most appropriate treatment for HRPC. Moreover, the majority of studies have shown that RP as monotherapy remains a viable option for the treatment of men with HRPC rather than RT and/or ADT therapy [7,12]. Mossanen et al. assessed 6477 patients with PC who underwent RP. Of the patients, 8.2% were at high risk according to the D'Amico risk classification, and the authors concluded that clinical stage T3 and high Gleason score were the most important prognostic factors for cancer-specific and OS [13]. Yossepowitch et al. evaluated 4,708 patients treated with RP alone, and argued that men with HRPC do not have a uniformly poor prognosis after surgery. Overall, 26% to 39% of the patients had an increased rate of adverse pathological features and the likelihood of BCR after the local therapy alone (HR 1.8 to 4.8) [14]. Spahn et al. analysed data from 1100 HRPC patients enrolled in a large multi-institutional study. Patients treated with RP alone remain clinical recurrence-free at long-term follow-up (10-year clinical recurrence-free survival rate: 87%) [15].

To our knowledge, there is no prospective randomized study to support the effectiveness of RP compared to other treatment modalities such as RT and/or ADT. Before the surgery, it is important to identify which HRPC patients might have favorable pathologic outcomes when surgically treated. Briganti et al. evaluated 1366 patients with HRPC who underwent RP and PLND. According to the number of preoperative high-risk features, they concluded that the rate of organ-confined disease and 10-yr BCR-free survival (1 vs.>1; 68.2% vs. 56.8, respectively p=0.03) were significantly decreased with the increasing number of preoperative risk factors [16]. The present study showed that there was a significant difference in progression rates of patients with 1vs 2-3 risk factors (12.4% vs. 26.5%, respectively) (p = 0.001). As the number of risk factors increased, pathological adverse features such as surgical margin positivity and lymph node invasion increased significantly, PFS was diminished, and additional treatment requirement was higher. (p=0.001, p=0.001, p=0.001, p=0.001, respectively) (Table 5).

According to European Association of Urology guidelines, PLND is recommended in patients with intermediate or high risk PC [9]. Although, it remains as the gold standard for staging in PC, its potential therapeutic value is still not clear. It has been shown in some studies that ePLND decrease cancer specific mortality compared with PLND [17-19]. However, others did not confirm this relationship [20,21]. More recently, a study by Preisser et al evaluated 9,742 patients who underwent RP with or without PLND, and they concluded that there was no significant difference in oncologic outcomes whether or not PLND was performed [21]. Similarly, our analysis demonstrated that PLND did not affect the progression rates after RP in both groups.

The surgical approach is another point of discussion. The guidelines have recommended that no surgical approach (open-, laparoscopic- or robot-assisted RP) has clearly superiority in terms of functional or oncological results. In a meta-analysis of 1485 patients where the PSA threshold for BCR was considered as > 0.2 ng /ml, robot-assisted RP was shown to have a lower risk of BCR compared to open RP (RR 0.71, 95% CI 0.61–0.81, I2 = 0%; p=0001). However, in a subgroup analysis at the long-term follow-up recurrence-free survival was similar in both surgical methods [22]. In a study of 1566 patients, 93% of the patients in open RP and 94% in laparoscopic and robot-assisted RP were without BCR. There was no statistically significant difference of biochemical free survival in different surgical methods (p=0.669). In this study, it was stated that the Gleason score and pathological stage played a

role as independent predictors of BCR [23]. Yaxley et al. evaluated the 326 men with localized PC who underwent robot-assisted RP or open RP in a randomized phase III trial [24]. They concluded that the robot-assisted arm has reduced admission times and blood loss at 12 weeks and, an updated analysis of this study has shown that these two techniques yield similar oncological and functional outcomes at 24 months [25]. Moreover, a recent Cochrane review assessed the effectiveness of laparoscopic or robot-assisted RP compared to open RP in men with localized PC. They found no significant difference in terms of oncological and functional outcomes. Robot-assisted and laparoscopic RP both resulted in statistically significant improvements in the duration of hospital stay and blood transfusion rates over open procedure [26]. It has also been shown that the success of RP depends on surgeon and hospital volume, and no surgical approach can be recommended over another [26-27]. In our study, total progression rates in open, laparoscopic, and robot-assisted surgery were 15.2%, 19.6%, and 17.5%, respectively, and there was no statistically significant difference between the three methods ($p = 0.22$). ePLND was performed more frequently in minimally invasive methods (laparoscopic and robot-assisted), thus the rate of lymph node invasion and overall progression was found to be significantly high in these patients ($p=0.001$, $p=0.001$)

High-risk patients are at risk of higher recurrence after definitive treatment, and there is growing body of evidence for multimodal treatment to achieve better long-term survival. Briganti et al. evaluated the current role of RP in 1366 patients with HRPC, and adjuvant therapy with either ADT or RT was used in 48% of all patients. The rate of adjuvant treatment was reported as 9 – 76% in the literature [19,28-30]. In our study, adjuvant therapy was not required in 74.7% of patients who underwent surgery. Adjuvant therapy, most frequently ADT, RT, and ADT + RT, were administered to 384 (25.3%) patients. Adjuvant therapy was significantly more common in patients with 2 or 3 risk factors compared to those with one risk factor (43.9% vs. 17.5%, respectively, $p=0.001$).

The limitations of our study are retrospective, non-randomized study design, and unidentified confounding variables that may have been present. Another significant limitation was the performance of procedures by multiple surgeons in thirteen different centers, and the individual learning curve and experience of each surgeon could be a source of bias. The year of treatment had a wide range, and it remains uncertain if patient selection and quality of medical care influenced the results. Moreover, another strong limitation of this study was the lack of central pathologic assessments. Furthermore, in

this study, all participants were followed by respective institutional protocols, and there was a lack of standardization for follow up.

Conclusions

RP alone (open, laparoscopic, or robot-assisted) is an effective treatment for most patients with HRPC. According to the number of preoperative high-risk features, as the number of risk factors increased, the need for additional treatment such as progression and ADT / RT increased, and these patients should be informed in detail in terms of multimodal treatment in the preoperative period. There was no significant difference in progression in patients with similar HRPC, whether PLND was or was not performed at RP. Prospective multi-institutional, randomized studies are required to determine the therapeutic value of PLND.

Ethics Approval:

The study was approved by the Ethics committee of Cukurova University (no: March 8, 2019;86/53)

Disclosure of interest:

The authors report no conflicts of interest.

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