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Radical Prostatectomy is a Valuable Treatment Alternative in Patients with High-Risk Prostate Cancer

Radikal Prostatektomi Yüksek Riskli Prostat Kanseri Hastalarında Değerli Bir Tedavi Alternatifidir

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What's known on the subject? and What does the study add?

There is no consensus regarding the optimal treatment of men with high-risk PCa and the current EAU and AUA guidelines recommend RP as a reasonable treatment option in selected patients. There is level 1 evidence suggesting that EBRT plus ADT is superior to EBRT alone in terms of overall survival (OS) and disease free survival (DFS) in patients with locally advanced PCa, but there is no level 1 evidence to recommend EBRT over RP. We reviewed the role of RP in comparison to EBRT in treatment of these patients in our patient cohort.

ABSTRACT

Objective

To review the high-risk prostate cancer (PCa) patient database with special emphasis on the role of radical prostatectomy (RP) in comparison to external beam radiotherapy (EBRT).

Materials and Methods

A total of 102 patients with complete and long-term follow-up data were included. High-risk PCa was defined as: a pre-treatment PSA level of ≥20 ng/mL and/or a primary Gleason score of ≥4 and/or clinical stage ≥T3N0M0 disease. A total of 45 (42.5%) patients underwent radical RP with extended pelvic lymphadenectomy for-high risk PCa and a total of 57 (53.8%) patients received EBRT.

Results

The mean overall survival (mean survival 95.2 vs. 129.2 months, log rank p=0.73) and cancer-specific survival (mean survival 104 vs. 151.4 months, log rank p=0.35) were not significantly different between RP and EBRT groups. Univariate analysis of variables that may affect overall survival showed no significant effect of pre-treatment PSA, Gleason score, clinical stage or type of therapy. The only factor which reached statistical significance was patient age (p=0.002). Multivariate analysis of variables also showed no significant effect of pre-treatment PSA, Gleason score, clinical stage or type of therapy and, again, the only factor which reached statistical significance was patient age (p=0.012).

Conclusion

Radical prostatectomy appears to be an effective and a non-inferior treatment option in patients with high-risk localized PCa with acceptable overall and cancer-specific survival compared to RT. Therefore, as the guidelines suggest, it should be provided as an option during patient consultation for a proper informed decision-making.

Key Words

High-risk prostate cancer, radical prostatectomy, radiotherapy, hormonal therapy

ÖZET

Amaç

Yüksek riskli prostat kanseri (YRPK) hasta veritabanını, ekstrenal radyoterapi ile karşılaştırılmalı olarak radikal prostatektominin rolünü vurgulayarak gözden geçirmektir.

Gereç ve Yöntem

Tam ve uzun dönemli takip verilerine sahip toplam 102 hasta çalışmaya dahil edildi. YRPK tanımı olarak; tedavi öncesi PSA değeri PSA ≥20 ng/mL ve/veya primer Glason skoru ≥4 ve/veya klinik TNM evresi ≥T3N0M0 kullanıldı. Toplam 45 (%42,5) hastaya radikal prostatektomi ve genişletilmiş pelvik lenfadenektomi ve toplam 57 (%53,8) hastaya da eksternal radyoterapi tedavisi uygulandı.

Bulgular

İki grup arasında ortalama genel sağkalım (95,2-129,2 ay, p=0,73) ve kansere özgü sağkalım (104-151,4 ay, p=0,35) arasında fark saptanmadı. Univariate ve multivaiate analizlerde genel sağkalım açısından sadece hasta yaşı anlamlı saptandı. Her iki analizde de tedavi öncesi PSA, Gleason skoru, klinik evre ya da tedavi şekli etkili olarak saptanmadı.

Sonuç

Radikal prostatektomi radyoterapi ile karşılaştırıldığında lokalize YRPK hastalarında kabul edilebilir genel ve kansere özgü sağkalım oranları ile etkin ve daha kötü olmayan bir tedavi seçeneğidir. Bu nedenle rehberlerin önerdiği gibi, uygun bir bilgilendirilmiş karar verme sürecinde hasta ile tedavi seçenekleri görüşülürken bir seçenek olarak sunulmalıdır.

Ahahtar Kelimeler

Yüksek riskli prostat kanseri, radikal prostatectomy, radyoterapi, hormon tedavisi

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Introduction

Due to widespread use of prostate-specific antigen (PSA) screening, the proportion of patients presenting with locally advanced prostate cancer (PCa) has been decreased in the last 20 years (1). However, high-risk disease is still not eradicated and comprises ≤15% of newly diagnosed cases in screened populations (2).

According to the widely accepted D'Amico risk stratification of PCa, high-risk disease is defined as a pre-treatment Gleason sum score of ≥8, or at least T2c clinical stage or a presenting PSA level of ≥20 ng/mL (3).

High-risk PCa is considered as a state of the disease where monotherapy will likely be insufficient for eradicating the tumor, since great majority of these cases are pathologically locally advanced with an increased likelihood of progressive and symptomatic disease or death from PCa (4). Although several primary treatment options, namely radical prostatectomy (RP), external beam radiotherapy (EBRT), brachytherapy, androgen deprivation therapy (ADT), and chemotherapy are available either alone or in combination, the optimal management remains controversial in this group of patients (5). Apparently, EBRT with or without ADT has been the most widely recommended modality. In the United States, the number of patients with locally advanced PCa, who were treated with EBRT, was 6.5 times more than that of those who were treated with RP after 2001 (6). The U.S. National Cancer Institute recommends EBRT plus (especially if there are no associated comorbidities) ADT as the first-line treatment for patients with locally advanced PCa (7), where RP is ranked as the third treatment option behind EBRT and EBRT plus ADT in these guidelines.

However, radical prostatectomy provides excellent local control of the primary tumor, accurately stages the disease to guide further therapy and removes benign sources of PSA, so that failures can be promptly identified and subsequent treatment can be initiated in a timely manner (8). Although traditionally not considered as the main treatment option in high-risk cases, the current European Association of Urology (EAU) and American Urological Association (AUA) guidelines recommend RP as an option in selected cases (9). There is level 1 evidence suggesting that EBRT plus ADT is superior to EBRT alone in terms of overall survival (OS) and disease-free survival (DFS) in patients with locally advanced PCa (10,11), but there is no level 1 evidence to recommend EBRT over RP. Thus, radical prostatectomy should be mentioned during patient counseling as a treatment option for men with high-risk PCa (8) in the multi-modality treatment era.

The aim of this study was to review our high-risk PCa patient database with special emphasis on the role of RP in comparison to EBRT in treatment of these patients.

Materials and Methods

Study Population

We retrospectively reviewed our database for patients treated and followed for high-risk PCa in, the department of urology, section of urooncology at Marmara University School of Medicine between 1993 and 2011. A total of 102 patients with complete and long-term follow-up data were included. High-risk PCa was defined as: a pre-treatment PSA level of ≥20 ng/mL and/or a primary Gleason score of ≥4 and/or clinical stage ≥T3N0M0 disease.

Tumors were classified according to the TNM classification system and histological grading was performed according to the Gleason scoring system. None of the patients had clinical evidence of distant metastasis or pelvic lymph node involvement on whole body bone scan, computed tomography of the abdomen and chest X-ray at the time of diagnosis.

Surgical Treatment

A total of 45 (42.5%) patients underwent radical retropubic prostatectomy with extended pelvic lymphadenectomy for-high risk PCa. All the operations were performed by a single surgeon (LT) with an open retropubic approach. Adjuvant therapy after radical prostatectomy was considered in patients with biochemical recurrence and/or adverse pathologic findings, such as seminal vesicle invasion, extra-prostatic extension and positive surgical margins. A total of 20 (44.4%) patients were given adjuvant hormone therapy (HT with or without chemotherapy in 9 (20%) and radiotherapy (RT) in 11 (24.4%) patients) at the discretion of the operating urooncologist.

Radiotherapy

A total of 57 (53.8%) patients received either 3-D conformal RT or intensity-modulated beam RT (IMRT). The target RT dose to be delivered was determined as at least 72 Gy and the patients were treated with 3D conformal RT until 2006 (n=37) and with IMRT thereafter (n=20). All patients received RT with adjuvant HT in the form of luteinising hormone-releasing hormone (LHRH) analogues.

Statistical Analysis

The Kaplan-Meier method was used in survival analysis. Differences in the observed survival between the groups were tested for statistical significance using the log-rank test.

Table 1. Patient characteristics

	Value n (%)
Age (years)	
Mean	66.4
Range	43-80
Clinical T stage (%)	
T3	16 (15.7)
<T3	86 (84.3)
Biopsy Gleason sum	
Mean	7.3
SD	1.0
Primer Gleason score	
Mean	3.7
SD	0.6
Pretreatment PSA (ng/mL)	
Median	24.1
Range	3.7-76
Treatment modality	
RRP	25 (24.5)
RT+HT	57 (55.9)
RRP+HT or CT	9 (8.8)
RRP+RT	11 (10.8)

PSA: Prostate-specific antigen, HT: Hormone therapy, RT: Radiotherapy, SD: Standard deviation

Results

The mean age of the study population was 66.4±6.7 years and the mean follow-up period was 44.1±40.2 months. The mean pre-treatment PSA level was 24.1±17.4 ng/mL and 16 of the patients had clinical stage T3 disease at the time of diagnosis. Other patient characteristics are shown in Table 1.

Pre-treatment patient characteristics were not significantly different between RP and RT groups in terms of Gleason score and clinical pT3 disease, but RP group seemed to be younger (63.6 vs. 68.7, p=0.001) and seemed to have a lower mean pre-treatment PSA (18.3 vs. 28.6, p=0.003) compared to RT group (Table 2).

The mean overall survival (mean survival 95.2 vs. 129.2 months, log rank p=0.73) and cancer-specific survival (mean survival 104 vs. 151.4 months, log rank p=0.35) times were not significantly different between RP and RT groups (Figure 1, 2). Five-year and 10-year overall survival and cancer-specific survival rates in the entire patient population were 76% vs. 89% and 57% vs. 67%, respectively.

Univariate analysis of the variables that may affect overall survival showed no significant effect of pre-treatment PSA, Gleason score, clinical stage or type of therapy (RP or EBRT). The only factor which reached statistical significance was patient age (p=0.002, Table 3).

Multivariate analysis of variables also showed no significant effect of pre-treatment PSA, Gleason score, clinical stage or type of therapy

Table 2. Comparison of group characteristics

	RRP (n=45)	EBRT+HT (n=57)	p value	Total
Age (years), mean (SD)	63.6 (6.1)	68.7 (6.3)	0.001	
Pretreatment PSA (ng/mL), mean (SD)	18.3 (13.3)	28.6 (19.0)	0.003	
Gleason sum score, mean (SD)	7.3 (1.0)	7.2 (1.0)	0.64	
Clinical stage, n (%)			0.19	
T3	5 (31.3)	11 (68.8)		16
<T3	40 (46.5)	46 (53.5)		86
Follow up (months), mean (SD)	58.7 (30)	46.9 (27)	0.06	

EBRT: External beam radiotherapy, HT: Hormone therapy, SD: Standard deviation

Table 3. Univariate analysis of factors that may effect overall survival

	Number of patients	Mean (±SE) months	95% CI	Log rank	Degree of freedom	p value
Age						
≤65	41	144.1 (±11.0)	122-165	4.9	1	0.02
>65	56	94.1 (±14.1)	66-121			
Gleason score						
<7	25	135.9 (±4.3)	107-164	1.5	1	0.21
≥7	72	105.8 (±12.4)	81-130			v
PSA at initial diagnosis						
<20	40	124.2 (±15.1)	94-153	0.12	1	0.72
≥20	53	119.9 (±12.1)	96-143			
Clinical T stage						
T3	16	120.3 (±19.0)	82-157	0.03	1	0.84
<T3	86	124.9 (±10.4)	104-145			
Type of treatment						
RRP	45	95.3 (±8.3)	78-111	0.11	1	0.73
RT+HT	57	129.2 (±12.2)	105-153			

PSA: Prostate-specific antigen, HT: Hormone therapy, RT: Radiotherapy

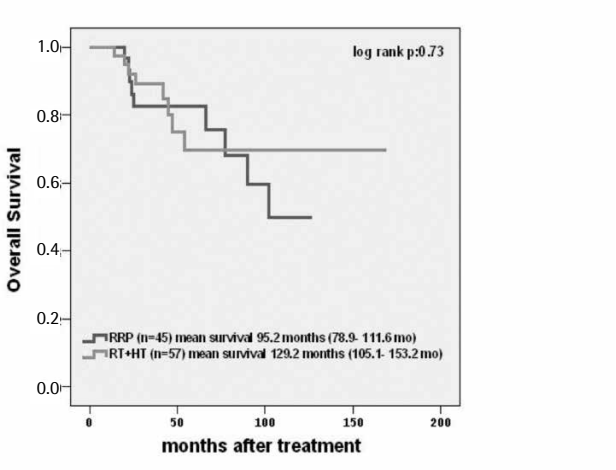

Figure 1. Kaplan meier analyses of overall survival between the groups

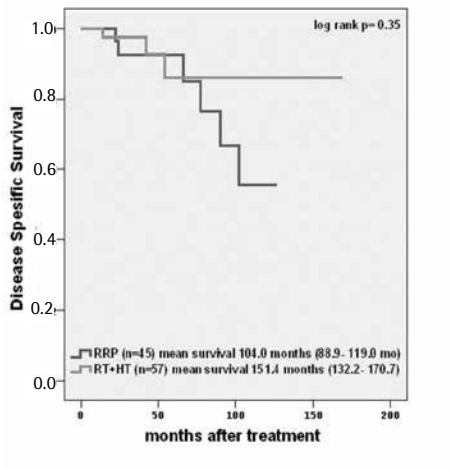

Figure 2. Kaplan meier analyses of cancer spesific survival between the groups

Table 4. Multivariate analysis of factors that may effect overall survival

	Coefficient of regression (B)	p	Exp (B) Odd's Ratio
Age (≤65 or >65 years)	-1.53	0.012	0.21
Gleason score (<7 or ≥7)	-0.71	0.220	0.48
PSA at initial diagnosis (<20 or ≥20 ng/mL)	-1.14	0.088	0.31
Clinical T stage (T3 or <T3)	-0.11	0.865	0.89
Type of treatment (RP or RT+HT)	-0.6	0.256	0.54

PSA: Prostate-specific antigen, HT: Hormone therapy, RT: Radiotherapy

(RP or EBRT). The only factor which reached statistical significance was patient age (p=0.012, Table 4).

Discussion

High-risk PCa is an aggressive disease and the treatment we perform should match this aggressiveness in order to achieve sufficient cancer control. In addition, personalized treatment for each patient should be planned for avoiding the possible side effects associated with over-treatment. Nearly half of our patients, who underwent RP, had to receive some kinds of adjuvant therapy either RT, HT or chemotherapy. From the urologist's point of view, in multimodality treatment of localized high-risk PCa, we would like to emphasize that salvage prostatectomy after RT is associated with higher incontinence and erectile dysfunction rates compared to salvage RT after RP (12). In the absence of randomized trials to define the ideal therapy for high-risk PCa, the mainstay of uro-oncologist's decision should be to reduce the risk of all-cause mortality while reducing cancer-related deaths.

Recently, Westover et al. (13) reported their PCa-specific mortality results comparing RP vs. combined-modality therapy (CMT) with brachytherapy, EBRT and HT in men with a Gleason score of ≥8 PCa using the data from 3 different centers . According to their results, after a median follow-up of 4.62 years, treatment with RP was not associated with an increased risk of PCa-specific mortality compared to CMT. Similarly, cancer-specific survival was also not significantly different between RP and RT groups in our patient population. Analysis of factors associated with an increased risk of PCa-specific mortality has been reported to be a baseline PSA value of <4 ng/mL and clinical stage of T2b and T2c (13). In our multivariate analysis, we found that only patient age was an independent variable that affects overall survival (Table 3). We observed that age-related health problems rather the type of the treatment (therefore, any possible difference in treatment success) were the main reason for death. Patient age was not found to have an effect on cancer-specific mortality (data not shown). A recent multi-center European study also addressed this issue where they examined cancer-specific and overall mortality rates in a large series of surgically managed high-risk PCa patients using a competing risks approach (14). The authors have reported that age and comorbidities were the major determinants of all-cause mortality and their impact on cancer-specific mortality was minimal. Survival rates in patients treated for high-risk PCa are consistent with our results, where the 10-year overall survival rates were between 52% and 77% and 10-year cancer-specific survival rates were between 66% and 91% (15,16,17).

There are some inherent drawbacks of this study related to its retrospective nature. Besides, being a single institution study, the patient population was highly selected which precluded the generalization of the results. The mean age as well as the mean pre-treatment PSA value in patients in our RP group was significantly less than in those in the RT group reflecting the nature of patient selection at our institution which hampers direct comparison of the treatment groups. Additionally, longer follow-up of patients in both treatment arms might have resulted in a significant difference in overall and cancer-specific survival. Another limitation is the absence of any final pathology report in EBRT group.

Radical prostatectomy appears to be an effective and a non-inferior treatment option in patients with a high-risk localized PCa with acceptable overall and cancer-specific survival compared to RT. Additionally, half of the patients can be spared adjuvant treatment. Therefore, as the guidelines suggest, it should be provided as an option during patient consultation for a proper informed decision-making.

Ethics Committee Approval: The study were approved by the Marmara University of Local Committee, **Informed Consent:** Consent form was filled out by all participants, **Concept:** Naşide Mangır, Levent Türkeri, **Design:** Naşide Mangır, İlker Tinay, **Data Collection or**

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