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

Naşide Mangir, Tuncay Top, İlker Tinay, Yıloren Tandır, Levent Türkeri

Marmara University Faculty of Medicine, Department of Urology, İstanbul, Turkey

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 PCs 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 PCs, 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 PCs 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 karşılaştırılarak radikal prostatektominin rolünü vurgulayarak gözden geçirmektir.

Gereç ve Yöntem
Tam ve uzun dönemli takip verilerine sahip toplam 102 hasta çalışmaya dahil edildi. Yüksek riskli PCa tanımı olarak; tedavi öncesi PSA değeri PSA ≥20 ng/mL ve/veya primer Gleason 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 sağkalım (ortalama 95,2 vs. 129,2 ay, p=0.73) ve kansere özgü sağkalım (ortalama 104 vs. 151,4 ay, p=0.35) arasında fark saptanmadı. Sadece hastanın yaşı etkili bulundu. salvol lara göre, p=0.002 olan ve diğerleri p=0.35 olan sonuçlar multivariat analizde de belirlenemedi. 

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 seçeneğini görüşülürken bir seçenek olarak sunulmalıdır.

Ahahtar Kelimeler
Yüksek riskli prostat kanseri, radikal prostatektomi, radyoterapi, hormonal tedavi
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>
<thead>
<tr>
<th>Table 1. Patient characteristics</th>
<th>Value n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>Mean 66.4</td>
</tr>
<tr>
<td></td>
<td>Range 43-80</td>
</tr>
<tr>
<td><strong>Clinical T stage (%)</strong></td>
<td>T3 16 (15.7)</td>
</tr>
<tr>
<td></td>
<td>&lt;T3 86 (84.3)</td>
</tr>
<tr>
<td><strong>Biopsy Gleason sum</strong></td>
<td>Mean 7.3</td>
</tr>
<tr>
<td></td>
<td>SD 1.0</td>
</tr>
<tr>
<td><strong>Primer Gleason score</strong></td>
<td>Mean 3.7</td>
</tr>
<tr>
<td></td>
<td>SD 0.6</td>
</tr>
<tr>
<td><strong>Pretreatment PSA (ng/mL)</strong></td>
<td>Median 24.1</td>
</tr>
<tr>
<td></td>
<td>Range 3.7-76</td>
</tr>
<tr>
<td><strong>Treatment modality</strong></td>
<td>RRP 25 (24.5)</td>
</tr>
<tr>
<td></td>
<td>RT+HT 57 (55.9)</td>
</tr>
<tr>
<td></td>
<td>RRP+HT or CT 9 (8.8)</td>
</tr>
<tr>
<td></td>
<td>RRP+RT 11 (10.8)</td>
</tr>
</tbody>
</table>

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.
Radical Prostatectomy for High-Risk Prostate Cancer

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- 

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
Processing: Tuncay Top, Yiğören Tanıdır, Analysis or Interpretation: Naşide Mangır, İlker Tinay, Literature Search: Naşide Mangır, Tuncay Top, Writing: Naşide Mangır, İlker Tinay, Levent Türkeri, Peer-review: Internal peer-reviewed, 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.

References