

Comparison of postoperative results in intermediate risk prostate cancer patients with radical prostatectomy

Radikal prostatektomi yapılmış intermediate risk prostat kanseri hastalarında postoperatif sonuçların karşılaştırılması

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ÖZET

Amaç: Bu çalışmada amacımız radikal prostatektomi yapılan intermediate risk grubu prostat kanseri hastalarını kılavuzlara göre alt gruplara ayırmak ve onkolojik, patolojik ve biyokimyasal sonuçlarını karşılaştırmaktır.

Gereç ve Yöntemler: 2016-2020 yılları arasında kliniğimizde prostat kanseri nedeniyle radikal prostatektomi yapılan intermediate risk grubundaki 36 hastayı retrospektif olarak değerlendirdik. Hastaları risk faktörlerine göre favourable ve unfavourable olmak üzere iki gruba ayırdık. Hastaların preoperatif prostat biyopsi ve radikal prostatektomi patoloji sonuçlarını, postoperatif 3. ve 6. ay kontrol PSA sonuçlarını, cerrahi sınır pozitiflik oranlarını, klinik ve patolojik evreler arasındaki farkları SPSS programını kullanarak istatistiki olarak karşılaştırdık.

Bulgular: Pozitif kor sayısı, postoperatif 3. ve 6. ay PSA değerleri, pozitif kor sayısı, cerrahi sınır pozitifliği, radikal prostatektomi sonrası upstage olma oranının unfavourable grupta daha yüksek olduğu tespit edildi. Bu farklar istatistiksel olarak anlamlı değildi. Pozitif kor yüzdesi ise unfavourable grupta istatistiksel olarak anlamlı şekilde daha yüksekti. (P<0,001)

Sonuç: Intermediate risk prostat kanseri heterojen bir hastalık grubudur. Tedavi rejimleri belirlenirken yaş, ek hastalık, hasta beklentisi gibi faktörler göz önünde bulundurularak seçim yapılması önem arz etmektedir.

Anahtar kelimeler: Prostat kanseri, PSA, Gleason skor, Intermediate risk

ABSTRACT

Objective: Our aim in this study was to separate the intermediate risk group prostate cancer patients who had radical prostatectomy in our clinic into subgroups according to NCCN Guidelines and compare their oncological, pathological and biochemical results.

Material and Methods: We retrospectively evaluated 36 patients in intermediate risk group who had radical prostatectomy in our clinic due to prostate cancer between 2016 and 2020. We separated the patients into two groups as favourable and unfavourable based on risk factors.

This study was approved by the Ethical Committee of Necmettin Erbakan University (Approval number: 2020/2719). All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

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We statistically compared preoperative prostate biopsy and radical prostatectomy pathology results, post-operative 3 and 6 month control PSA results, surgical border positivity ratios and the differences between clinical and pathological stages of the patients using SPSS program.

Results: Positive core number, post op. 3rd and 6th month PSA values, positive core count, surgical border positivity, post radical prostatectomy upstaging ratio were detected higher in unfavourable group. These differences were statistically insignificant. Positive core percentage was statistically significantly higher in unfavourable group ($P < 0.001$).

Conclusion: Intermediate risk prostate cancer is a heterogeneous disease group. Treatment regimens should be selected by considering factors such as age, additional disease and patient expectation.

Keywords: Prostate cancer, PSA, Gleason score, Intermediate risk

INTRODUCTION

Prostate cancer is the most common non-cutaneous malignancy in males. They constitute 27% of all cancers (1). According to National Comprehensive Cancer Network (NCCN), they are classified under three groups as diseases with low, intermediate and high risk in terms of histological characteristics and prognosis (2). Intermediate disease is quite heterogeneous; biochemical and clinical recurrence ratios may change between 2 to 70%. (3,4)

Intermediate disease was separated into two different classes in time due to heterogeneous tumor characteristics and variable oncological results. Zumsteg et al. suggested separating intermediate risk group patients into the subgroups of favourable and unfavourable depending on primary Gleason pattern, percentage of positive prostate biopsy cores and the number of intermediate risk group factors. This suggestion was supported by different studies and was covered in NCCN, AUA and ASTRO guidelines. (2,5,6) But American Urological Association (AUA) didn't include biopsy core involvement in this classification. (6)

Our aim in this study was to separate the intermediate risk group prostate cancer patients who had radical prostatectomy in our clinic into subgroups according to NCCN Guidelines and compare their oncological, pathological and biochemical results.

MATERIAL AND METHODS

A total of 36 intermediate risk group patients according to NCCN guidelines who had radical prostatectomy due to prostate cancer in our clinic between 2016 and 2020 were included in the study and data were retrospectively examined. This study was approved by the Ethical Committee of Necmettin Erbakan University (Approval number:2020/2719) and ethical standards described in the Helsinki Declaration Statement have been followed in this study.

As defined by NCCN Guidelines, Gleason grade group 1 or 2 (3+3 or 3+4) patients with only one intermediate risk factor (T2b-T2c, Gleason 7 and PSA 10-20 ng / ml) and <50% core positivity in biopsy were defined as the favourable group while Gleason grade group 3 patients with 2 or 3 intermediate risk factors and > 50% positivity in biopsy were defined as the unfavourable group. (Table 1).

Patients were classified under two groups as favourable (Group-1) and unfavourable (Group-2). Preoperative prostate biopsy pathology results and radical prostatectomy pathology results of the patients were compared and the differences between 3rd and 6th month control PSA results, surgical border positivity ratios and pathological stages were evaluated.

RESULTS

There were 19 patients in Group 1 (Favourable) and 17 patients in Group 2 (Unfavourable). Mean ages were similar in the groups. (62.8 vs 64.5).

Preoperative PSA values of the patients were statistically significantly lower in Group 1. ($p < 0.01$). Although there was no significant difference between the groups in the postoperative 3rd and postoperative 6th PSA values, it was lower in Group 1.

According to the radical prostatectomy pathology evaluation, one patient in the Group 1 had positive surgical margins, while five patients in Group 2 had positive surgical margins (p:0.10). When the groups were compared for positive core percentages, the mean percentage was detected as 25.2% for Favourable group and as 62.1% for Unfavourable group (p<0.01). Although positive core number was higher in the unfavourable group, it wasn't statistically significant (p:0.35).

Clinical stages of patients were compared with postoperative pathological stages. Upstaging ratio was 31% in favourable group (6/19) while it was 43% (7/17) in unfavourable group. While downstaging is observed in the pathological stage in nearly 10% (2/19) of the patients in favourable group, this ratio was nearly 6% (1/17) in the unfavourable group.

Pathological and biochemical parameters of intermediate subgroups are available in Table 2.

Table 1: National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology: prostate cancer(NCCN 2019)

Intermediate risk Prostate Cancer	Has all of the following:	Favourable Intermediate	Has all of the following:
	<ul style="list-style-type: none"> No high/very high-risk group features Has one or more intermediate risk factors <p>-T2b-T2c -Gleason 7 -PSA 10-20 ng/ml</p>	Unfavourable Intermediate	<ul style="list-style-type: none"> 1 Intermediate risk factor Grade group 1 or 2 <%50 biopsy cores positive <p>Has one or more of the following:</p> <ul style="list-style-type: none"> 2 or 3 intermediate risk factors Grade group 3 >%50 biopsy cores positive

Table 2. Biochemical, pathological and oncological parameters belonging to the intermediate subgroup

	Favourable group (n:19)	Unfavourable group (n:17)	p
Age(years)	62,8±5,3	64,5±4,5	0,30
PSA Before Prostate Biopsy (ng/ml) (mean±SD)	7,9±3,3	12,8±3,9	0,0001
Postoperative 3rd month PSA (ng/ml) (mean±SD)	0,05±0,07	0,15±0,38	0,30
Postoperative 6th month PSA (ng/ml) (mean±SD)	0,07±0,10	0,18±0,33	0,17
Number of Positive Cores	3,3±1,8	3,8±1,7	0,35
Positive Cor Percentage(%)	25,2±14,8	62,1±23,5	0,0001
Number of Patients with Surgical Border Positive n(%)	1(%5,2)	5(%29,4)	0,10

Prostate biopsy (ISUP Grade) n(%)	1	2				1	2			3	
	14 (%38,8)	5 (%13,8)				4 (%11,1)	12 (%33,3)			1 (%2,7)	
Radical Prostatec- tomy pathology (ISUP Gra- de) n(%)	1	2	3	4	5	1	2	3	4	5	
	7 (%36,8)	9 (%47,3)	1 (%5,2)	1 (%5,2)	1 (%5,2)	5 (%29,4)	7 (%41,1)	4 (%23,5)	0	1 (%5,8)	
Upstage after Radical Prostatectomy n(%)	6(%31)					7(%43)					

DISCUSSION

Prostate cancer is an important health service problem as it is the most common solid cancer. (7) Curative treatment is possible when the disease is in local stage. Patients are classified according to risk groups during local staging. Being able to determine recurrence possibility after treatment and to choose the suitable treatment constitute the aim of risk classification.

Different treatment modalities are available for prostate cancer treatment. Age, curability, comorbidity and 10-year survival chance are among important criteria for choosing the suitable treatment for the patient. Active surveillance, radical prostatectomy, radiotherapy and ablative treatments are among treatment options.

D'Amico classification defined by D'Amico et al in 1998 is one of the first and still most commonly used classification methods for localized prostate cancer patients. (4) D'Amico classification is based on Gleason score, PSA and clinical stage. According to this, intermediate risk patients are defined as patients meeting at least one of these criteria: Gleason 7, T2b clinical stage and PSA level between 10 and 20.

But heterogeneous distribution and progression difference in intermediate group was observed in time. Thus NCCN Guidelines separated intermediate prostate cancer patients into two separate groups.

In a retrospective analysis performed by Zumsteg et al using SEARCH database, biochemical recurrence, metastasis and post-radical prostatectomy pathological upstaging risk was detected higher in intermediate patients in unfavourable risk group treated surgically. In this study, cancer specific death risk was also found to increase in patients with 2 or more unfavourable risk factors. (8)

All of the five patients with surgical border positivity in unfavourable risk group had 2 or 3 unfavourable risk factors in our study. (p:0.049) In this regard, when we compared the patients who have one unfavourable risk with those who have multiple unfavourable risks, we think that the clinical progression is higher in multiple risk factor group and this patient group constitutes the most suitable patients for radical prostatectomy.

In a review which evaluated 1159 prostate cancer patients who had radical prostatectomy in 2015, 5 year biochemical recurrence-free survival was found statistically significantly higher in favourable patient group compared to the unfavourable group. (5) (87.5% vs 66.5%) (p<0.001). Although long-term follow-up is required for our study, while the biochemical recurrence-free survival was 78% in the favourable group and 76% in unfavourable group based on postoperative 3th month biochemical recurrences and this difference wasn't statistically significant. This situation can be explained by the low number of our patients.

Active surveillance is a preferred method in very low and low risk prostate cancer. (9) Active surveillance can also be considered in suitable intermediate risk patients (10). These suggestions actually depend on ProtecT study. In this study, 1643 localized prostate cancer patients were followed-up with radical prostatectomy, radiotherapy and active surveillance. After an average follow-up duration of 10 years, a significant difference specific for prostate cancer couldn't be found among three treatments. Lower disease

progression and distant metastasis were observed in the surgery and radiotherapy. (11) Active surveillance is applied in low and very low risk prostate cancer patients in our clinic. Considering that the patients in this study are in intermediate risk group and there can be an increase in progression risk and mortality risk, radical prostatectomy was preferred for treatment in these patients.

In a prospective study made by Klotz, patients with a favourable risk, older than 70 years old, with less than 15 PSA value, less than 10 years life expectancy and comorbidities were included in the study. (12) In a mean follow-up duration of 6.4 years, metastasis occurrence ratio was detected as 2.8% and prostate cancer related death ratio was 1.5%. This study shows that active surveillance can be a safe method in selected intermediate risk prostate cancer patients. Only four patients in our study were over 70 years old and 32 of them were 70 years old or younger. Active surveillance wasn't preferred since 10 year survival expectancy of the patients was high.

Radical prostatectomy is one of the surgeries used in prostate cancer treatment for many years. Providing of long term cancer control, prognosis prediction through pathological staging, follow-up easiness provision through PSA, relief of obstructive symptoms and applicability of adjuvant radiotherapy in local recurrence are among its advantages. (13) It also provides psychological relief in the patient as the cancer tissue will be removed.

Based on the study by Scandinavian Prostate Cancer Group (SPCG), radical prostatectomy is a treatment option suggested for intermediate risk prostate cancer patients with life expectancy over 10 years. (14) While death risk due to prostate cancer was 19.6% in radical prostatectomy group, it was reported as 31.3% in observation group in the study. (15) Based on PIVOT study, prostate-cancer related mortality was lower in radical prostatectomy compared to the observation group. (16) When the radical prostatectomy pathologies of our patients were examined, 1 patient in favourable risk group and 5 patients in unfavourable group had surgical border positivity (p: 0.10) This showed us that surgical border positivity can be high especially in patients in unfavourable group even in case of a surgery and thus this group of patients are more risky in terms of extraprostatic extension.

Until now, no prospective study comparing radiotherapy and radical prostatectomy has been reported in intermediate risk patients. Thus retrospective studies are used to be able to compare radiotherapy in this patient group. In a metaanalysis, mortality ratio was detected lower in patients who had radical prostatectomy compared to those treated with radiotherapy. (17) However, in these studies, the reliability of the studies decreases due to the differences in the application of Androgen Deprivation Therapy (ADT) in the heterogeneity and radiotherapy group. Radiotherapy should be given in IMRT (intensity-modulated radiotherapy) form in a hypofractionated program combined with short-term (3-6 months) ADT especially in the unfavourable group. (18) Radiotherapy wasn't preferred for the patient group in our study due to high life expectancy and surgery demand. These patients were also provided the information that they have adjuvant radiotherapy option in possible biochemical recurrence and surgical border positivity conditions following radical prostatectomy. Close PSA follow-up was performed in the patients who had radical prostatectomy and radiotherapy and/or ADT treatments were suggested to the patients in surgical border positivity and/or early biochemical recurrence conditions.

Radical prostatectomy is considered as a prominent treatment method especially in young patients and patients without comorbidities. Prostate cancer detected patients younger than 55 years of age were separated into three groups in a study the results of which were published in February 2020. (Group 1:Radical prostatectomy, Group 2:Radiotherapy, Group 3: Radiotherapy+ADT). Cancer-free survival ratios of the patients in a 59 month follow-up were detected as 94.2%, 85.2% and 80.7% respectively. (19) Since 70% of the patients in our study are under 65 years of age and have high life expectancy, radical prostatectomy was suggested and applied to achieve high cancer-free survival ratios as stated by Chua et al.

To sum up, it was observed in our study that upstaging following radical prostatectomy could occur in favourable patients as much as unfavourable patients. Upstaging ratio was 31% in favorable group (6/19) while it was 41% (7/17) in unfavourable group. While downstaging is observed in the pathological stage in nearly 10% (2/19) of the patients in favourable group, this ratio was nearly 6% (1/17) in the unfavourable group. Although biochemical and pathological parameters had a more aggressive presentation in unfavourable group as expected, we think that this mostly insignificant difference can be related to limited patient population.

CONCLUSION

Radical prostatectomy is an effective treatment modality with many advantages and urologists have more experience of it in prostate cancer treatment compared to non-surgical methods. It can be safely applied in patients who especially have long life expectancy and no comorbidity in intermediate risk group.

Subgroups must be determined during the treatment selection and regulation in intermediate risk group patients diagnosed with prostate cancer. We think that it would be more correct to decide the treatment modality which would minimize PSA recurrence and surgical border positivity together with the patient, considering other conditions such as age, additional diseases and patient expectation.

Ethical Approval: This study was approved by the local ethical committee (Approval number: 2020/2719). All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

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