Original Article

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Radical Prostatectomy Outcomes in Patients with Clinical Lymph Node Involvement from The Turkish Urooncology Database

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Abstract

Objective: This study aimed to investigate pathological lymph node involvement in selected patients and the relationship of prostate-specific antigen (PSA) progression-free survival rates between patients with and without lymph node involvement on preoperative conventional radiologic imaging. Limited data is available about local treatment outcomes in patients with prostate cancer (PCa) having clinical lymph node involvement.

Materials and Methods: Using the national PCa database, patients who underwent radical prostatectomy (RP) and pelvic lymph node dissection between 2001 and 2019, with pathologic lymph node involvement, were included in the study. Patients were divided into two groups as those with and without clinical lymph node involvement by preoperative imaging.

Results: A total of 213 patients were included in the final analysis, wherein 164 are with and 49 are without lymph node involvement. After the mean follow-up periods of 33.9 months, a significant difference was not found between the two groups in terms of recurrence, adjuvant treatment necessity, and final status. The multivariate analysis for 5-year PSA recurrence-free survival revealed that surgical margin positivity was the only significant factor (p=0.016, hazard ratio: 2.67, confidence interval: 1.19-5.98).

Conclusion: Our results revealed that preoperative clinical lymph node status did not affect the 5-year PSA recurrence-free survival in pathologic lymph node involvement of patients treated with RP and pelvic lymph node dissection. Therefore, RP stands as an effective treatment option in selected patients with PCa having clinical lymph node involvement.

Keywords: Metastases, prostate cancer, radical prostatectomy, recurrence-free survival, surgical margin positivity

Introduction

The first treatment recommended in the early stage or localized prostate cancer (PCa) is radical prostatectomy (RP) according to European Association of Urology (EAU) guidelines, especially in intermediate and high-risk patients (1). Historically, patients with lymph node involvement were not operated two decades ago; however, this approach has changed in the last decade, as increased long-term survival rates with RP (2) and extended lymph node dissection were reported in such patient groups (3,4,5). In recent years, a more extensive lymphadenectomy during RP should be performed (6,7,8,9,10). Thus, with

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growing evidence, the latest EAU Guidelines updated to offer RP to selected patients with any clinical N1 as part of multimodal therapy with a strong recommendation, whereas the National Comprehensive Cancer Network (NCCN) guidelines still do not mention surgery in patients with clinical N1 as an option (1,11). A brief correspondence by Moschini et al. (2) reported that clinical lymph node metastases were not a factor in survival determination after RP and pelvic lymph node dissection (PLND) in patients with PCa.

This study investigated the difference in prostate-specific antigen (PSA) progression-free survival rates between patients with and without cN+ disease on preoperative conventional radiologic imaging in patients with pathologically pelvic lymph node metastasis positive (pN+) PCa at RP and PLND.

Materials and Methods

Patient Population

Patients in the database of the Turkish Urooncology Association, who underwent RP and PLND between 2001 and 2019 with pathological lymph node involvement, were included in the study. The study protocol was reviewed and approved by the Institutional Review Board of Marmara University Faculty of Medicine (approval number: 09.2020.639). Patient data from 10 different centers, whose lymph node involvement status was evaluated with preoperative imaging using computed tomography (CT) and/or magnetic resonance imaging (MRI), were recorded. In addition, all bone scan results were negative. The clinical lymph node involvement was defined as malignant if the long axis of the node was >10 mm. Patients were divided into two groups as those with (cN+) and without (cN-) clinical lymph node involvement according to CT and/or MRI results.

Patient Inclusion-Exclusion Parameters

Patients with non-regional lymph node metastasis (M1a), who received preoperative hormonal treatment and/or radiotherapy (RT) and those previously diagnosed with other cancers and non-adenocarcinoma PCa, were excluded. Preoperative age and PSA level, biopsy Gleason grade group, clinical stage, type of operation (open, laparoscopic, and robotic), the total number of lymph nodes removed, the total number of positive lymph nodes, lymph node density, prostatectomy Gleason grade group, pathological stage, surgical margin status, extracapsular extension, seminal vesicle invasion, follow-up time, time to PSA progression, type of adjuvant therapy, postoperative PSA level, and last status (alive or dead), were retrospectively recorded. A total of 10 participating centers are experienced centers in urooncological surgery in our country. Standard lymphadenectomy is defined as extended in the form of fatty tissue removal around the pelvic lymph node borders, including the obturator fossa, internal and external iliac, common iliac vessels, and presacral nodes in some selected cases.

Statistical Analysis

The cN+ and cN- groups were compared in terms of age, preoperative and postoperative PSA levels, biopsy and prostatectomy Gleason grade groups, lymph node density, total and positive lymph node numbers, and time to PSA progression using the Mann-Whitney test. The terms of clinical stage, type of surgery, pathologic stage, surgical margin status, extracapsular extension, seminal vesicle invasion, and last status were analyzed using the χ^2 test. The Kaplan-Meier analysis was used to analyze the time to PSA progression between the two groups. Multivariate analysis including RP T-stage, RP Gleason grade group, the total number of lymph nodes removed, the number of positive lymph nodes removed, lymph node density, surgical margin status, and clinical lymph node positivity parameters were performed for the 5-year PSA relapse-free survival.

Results

Initially, 230 patients with pathologic lymph node involvement were included in the study, and 213 with adequate data and a follow-up period of at least 3 months were included for further assessment. Among these 213 patients, 164 patients with clinical lymph node involvement (cN+) and 49 patients without clinical lymph node involvement (cN-), were divided into two groups according to preoperative imaging. The mean and median preoperative PSA values were 23.34 and 14 ng/mL, respectively. The mean and median follow-up periods of patients were 33.9 and 28 months, respectively, ranging from 3-153 months. Comparison of the two groups revealed that EAU high-risk group was significantly higher in the cN+ group ($p<0.05$), without difference in other parameters (Table 1).

A total of 8 deaths were detected in the patient data, and 1 patient in the cN- group died of PCa. No significant difference was reported between the two groups in terms of recurrence, adjuvant therapy, end status, and time to PSA progression. (Table 2) An overall and cancer-specific survival analysis was not performed as a very limited number of deaths and a short follow-up period were observed. Instead, time to PSA progression was examined using the Kaplan-Meier analysis between the two groups, which revealed no significant differences ($p=0.865$; Figure 1).

The multivariate analysis for 5-year PSA recurrence-free survival revealed surgical margin positivity as the only significant factor ($p=0.016$, hazard ratio: 2.67 confidence interval: 1.19-5.98). The multivariate analysis revealed that factors, such as clinical lymph node involvement, pathological tumor stage, pathological Gleason grade group, adjuvant therapy, positive lymph node number, and lymph node density, do not affect 5-year PSA recurrence-free survival (Figure 2).

Discussion

Our study results found no significant difference in the time to PSA recurrence in patients with pathologically positive lymph nodes in the specimen of extended lymphadenectomy, whether or not these patients had cN+ or cN0 disease. For the first time, Moschini et al. (2) reported that clinical lymph node metastasis was not a determining factor after RP and PLND in such a situation and concluded that it is not an absolute surgical contraindication. To our knowledge, this is the second study in the literature that revealed that in appropriately selected cN+ patients, RP, and extended PLND revealed a similar time to PSA progression rates compared to cN0 patients. A study

Table 1. Descriptive statistics classified according to clinical node status				
	Overall (n=213; 100%)	**Clinical N+ (n=164; 77%)**	**Clinical N- (n=49; 23%)**	**p-value**
Age at surgery				
Mean	63.02	63.08	62.91	0.899
Median	64 (42-78)	61 (42-78)	63 (46-75)	
Follow-up time (month)				
Mean	33.9	34.9	30.5	0.320
Median	28 (3-153)	28 (3-153)	24 (4-120)	
Preoperative PSA				
Mean	23.34	24.84	18.32	0.052
Median	14 (1.01-203)	14.84 (1-203)	13 (4.2-96)	
EAU risk groups				
Low-risk	5 (2.3%)	2 (1.2%)	3 (6.1%)	<0.05
Intermediate-risk	18 (8.5%)	8 (4.9%)	10 (20.4%)	
High-risk	190 (89.2%)	154 (93.9%)	36 (73.5%)	
Positive nodes				
Mean	2.74	2.90	2.22	0.112
Median	2 (1-36)	2 (1-36)	1 (1-10)	
Nodes removed				
Mean	17.48	18.16	15.22	0.124
Median	15	16 (2-77)	13 (1-62)	
Lymph node density				
Mean	0.197	0.182	0.248	0.094
Median	0.133	0.125 (0.02-0.90)	0.187 (0.02-1.0)	
Pathologic stage				
pT2	14 (6.5%)	11 (6.7%)	3(6.1%)	0.628
pT3a	54 (25.3%)	39 (23.7%)	15 (30.6%)	
pT3b	145 (68%)	114 (69.5%)	31 (63.2%)	
Pathologic Gleason grade group				
1	5 (2.3%)	3 (1.8%)	2 (4%)	0.602
2	27 (12.6%)	22 (13.4%)	5 (10%)	
3	55 (25.8%)	39 (23.7%)	16 (32%)	
4	36 (16.9%)	28 (17%)	8 (16.3%)	
5	90 (42.2%)	72 (43.9%)	18 (36.7%)	
Positive surgical margin	153 (71.8%)	120 (73.1)	33 (67.3%)	0.426
Adjuvant hormonal therapy	91 (42.7%)	70 (42.6%)	21 (42.8%)	0.145
Adjuvant radiotherapy	56 (26.2%)	38 (23.1%)	18 (36.7%)	
EAU: European Association of Urology, PSA: Prostate-specific antigen				

by Moschini et al. (2) reported cancer-specific survival rates at their long follow-up period. Our mean follow-up time was 33.9 months and cancer-specific survival data were limited for appropriate evaluation, as our death numbers were low in this relatively limited follow-up period.

In cN+ patients, Seisen et al. (7) reported that almost two-thirds received local therapy (surgery or RT) with or without androgen deprivation therapy (ADT). They also emphasized that patients who received local therapy had significantly lower mortality rates than patients who only received ADT (7). This study

Table 2. Comparison of patients with and without clinical lymph node involvement				
		Clinical N+	**Clinical N-**	**p**
Recurrence	Yes	44 (26.83%)	12 (24.49%)	0.744
	No	120 (73.17%)	37 (75.51%)	
Adjuvant treatment	Yes	120 (73.17%)	39 (79.59%)	0.365
	No	44 (26.83%)	10 (20.41%)	
End status	Dead	6 (3.66%)	2 (4.08%)	0.891
	Alive	158 (96.34%)	47 (95.92%)	

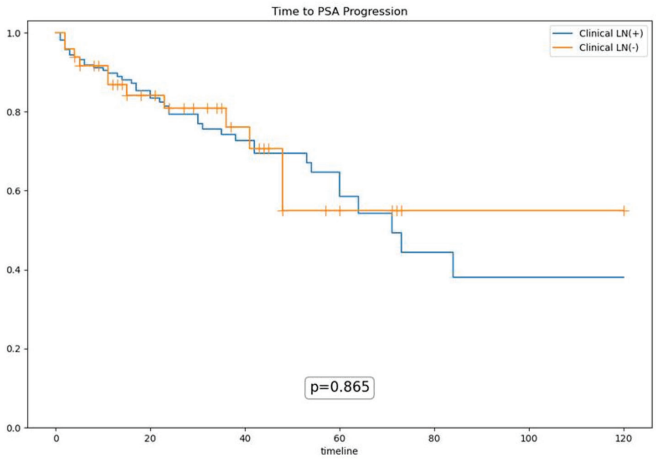

Figure 1. Kaplan Meier analysis between the two groups in terms of time to PSA progression

PSA: Prostate-specific antigen

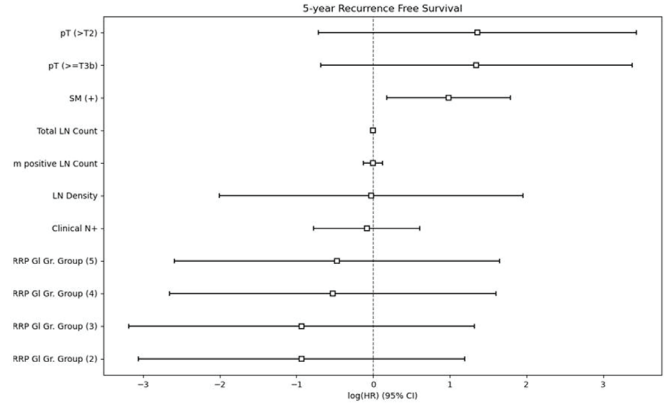

Figure 2. Multivariate analysis of the 5-year PSA recurrence-free survival

PSA: Prostate-specific antigen

revealed an RP ± ADT survival benefit compared to RT ± ADT but was not statistically significant, and 37.8% of their patients were treated with RP + ADT. In our study, the adjuvant ADT ratio was 42.7% and was very similar to the rate of Seisen et al. (7). The additional adjuvant ADT generally depends on the treating Urologist's choice.

The EAU risk classification was used in our study, whereas Moschini et al. (2) used NCCN risk grouping in their study. Of our patients, 89.2% were in the high-risk group, whereas the in Moschini et al.'s (2) study was 64.5%. Our study included predominantly more high-risk patients compared to Moschini et al.'s (2) study, and the time to PSA recurrence was not different in cN+ and cN- patients, which proposes a similar clinical course, following Moschini et al.'s (2) findings.

In our study, cN+ patients had higher positive lymph node counts; however, positive lymph node count and lymph node density were not statistically different between the two groups. While, in Moschini et al.'s (2) study, a statistically significantly higher number of positive lymph nodes were reported in the cN+ group compared to that of the cN- group (2). In our study, the mean and median of the total number of removed lymph nodes was higher than Moschini et al.'s (2) study, which explains the different findings.

Prostatectomy Gleason grade groups and its parameter were similar in our study and Moschini et al.'s (2) study results, wherein significant difference was not found between the groups. Contrarily, Moschini et al. (2) reported that taking pathologic Gleason score 2-6 as a reference, pathologic Gleason score of 8-10 versus 6 was a significant predictor of cancer-specific mortality (p=0.04). Today, pathologic Gleason score of <6 is not an acceptable pathological finding, and in our study, only 2.3% of our pLN+ cases had pathologic Gleason grade group. Contrarily, 17.2 % of patients in Moschini et al.'s (2) study had pathologic Gleason score of 2-6, which explains the difference between the two studies. Moreover, no difference was found between the groups in terms of surgical margin positivity, adjuvant hormonal therapy, and adjuvant RT in both studies. A small number of patients received neoadjuvant hormonal therapy in the study of Moschini et al. (2), and this rate was significantly higher in the group with clinical lymph node involvement. Patients who received neoadjuvant hormonal therapy were excluded from our study to create a more homogeneous patient population.

The multivariable analysis performed in Moschini et al.'s (2) study reported that some positive lymph nodes and Gleason grade group of 8-10 were predictors for cancer-specific mortality compared to 6 or less, and clinical lymph node involvement was not a predictive factor. Similar to that study, we found that clinical lymph node involvement did not affect the 5-year PSA recurrence-free survival. While surgical margin positivity was the only significant factor in multivariable analysis.

Study Limitations

Our study has some limitations. Our results were derived from retrospective data of 10 different centers. The patient follow-up period was short, thus the time to PSA progression was examined, and cancer-specific and overall survival rates were not reported. With a longer follow-up period, we hope to report these results, as well. Centralized pathology was not available in our study but all 10 academic centers had their experienced uropathologists.

Conclusion

Our results revealed that, in pN+ patients who were treated with RP and PLND, preoperative clinical lymph node status (cN+ or cN-) did not affect the 5-year PSA recurrence-free survival. Therefore, in selected patients with PCa with cN+ disease, RP is an effective treatment option.

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Ethics

Ethics Committee Approval: The study protocol was reviewed and approved by the Institutional Review Board of Marmara University Faculty of Medicine (approval number: 09.2020.639).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: H.H.T., O.E., T.M., S.B., Design: H.H.T., O.E., T.M., S.B., Data Collection or Processing: H.H.T., O.E., B.A., V.İ., U.Y., S.S., G.A., B.Ş., İ.T., T.M., S.B., Analysis or Interpretation: H.H.T., O.E., B.Ş., Literature Search: H.H.T., S.B., Writing: H.H.T., İ.T., S.B.

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