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Does Limited Pelvic Lymphadenectomy in Low-Risk Prostate Cancer Patients Affect Biochemical Recurrence?

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ABSTRACT

Introduction: Several studies have reported a very low incidence of lymph node metastasis in D'Amico low-risk prostate cancer. As a result, omission of the pelvic lymphadenectomy (PLND) has become more common in this group. We evaluated whether omission of a PLND in these patients was associated with increased rates of 5-year biochemical recurrence (BCR).

Materials and Methods: The study population included 535 patients with prostate cancer clinical stage T1-2, Gleason 3 + 3, and PSA < 10 ng/mL. Patients were divided into 2 groups, those with a limited PLND (+PLND) at the time of prostatectomy (N = 139) and those without (–PLND) (N = 396). BCR was defined as PSA > 0.2 ng/mL at any time following surgery. Univariate and multivariate Cox proportional hazards analyses were applied to evaluate the association between the omission of PLND and BCR.

Results: Median follow-up was 43 months (range 0.4 to 194.8). The mean number of lymph nodes obtained at PLND was 6.2 (range 1 – 38). Of these, 122 men had BCR during follow-up. Men who had PLND had earlier surgery dates and were more likely to have had open prostatectomy. They were also associated with higher preop PSAs, fewer biopsy cores but a higher percent of positive cores, and higher maximum cancer in any 1 core. Kaplan-Meier analysis revealed similar survival curves for both groups (log-rank test P = 0.723). Using the univariate Cox proportional hazards analysis, omission of PLND was not associated with a higher risk of BCR when compared to +PLND. Preoperative PSA, year of surgery, procedure type, pathologic Gleason score and stage, as well as margin status were all significantly (P < 0.05) associated with the risk of BCR, while African American race approached significance (P = 0.062).

Conclusion: With a 43-month median follow-up, D'Amico low-risk prostate cancers are no more likely to develop BCR when limited PLND is omitted than those who undergo limited PLND. A potentially confounding variable might be the variability in the extent of PLND.

INTRODUCTION

Several studies report a very low incidence of lymph node metastasis in low-risk prostate cancer, and pelvic lymphadenectomy (PLND) is decreasing in this group [1-3]. Evidence suggests that it can be safely omitted in patients who are D'Amico low-risk without putting the patient at risk for biochemical recurrence [4-6]. Based on commonly used nomograms, a patient with D'Amico low-risk prostate cancer has an approximately 2% chance of having lymph node

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Table 1. Demographic, preoperative clinical, and pathological characteristics by pelvic lymph node dissection status.

	Pelvic Lymph Node Dissection		P Value
	Yes (N = 139)	No (N = 396)	
Age at surgery	59.1 ± 6.4	59.3 ± 6.8	0.785
Race			
- White	96 (69%)	289 (73%)	
- Black	36 (26%)	88 (22%)	
- Other/unknown	7 (5%)	19 (5%)	0.660
Year of surgery			
- 1990-1996	28 (20%)	8 (2%)	
- 1997-2000	41 (30%)	40 (10%)	
- 2001-2003	34 (24%)	110 (28%)	
- 2004-2006	36 (26%)	238 (60%)	< 0.001
Preoperative PSA (ng/mL)	5.6 ± 2.2	5.1 ± 1.9	0.009
Prostatectomy type			
- RARP	29 (21%)	199 (50%)	
- LRP	5 (4%)	38 (10%)	
- ORP	105 (76%)	159 (40%)	< 0.001
Clinical tumor stage			
- T1	113 (81%)	341 (86%)	
- T2	26 (19%)	55 (14%)	0.173
Pathological Gleason score			
- ≤ 6	98 (71%)	287 (72%)	
- 7+	41 (29%)	109 (28%)	0.656
Pathological tumor stage			
- ≤ T2	108 (78%)	319 (81%)	
- T3+	31 (22%)	75 (19%)	0.407
Positive margins	38 (28%)	96 (38%)	0.634
Number of cores (N = 437)	9.4 ± 4.1	11.0 ± 3.8	< 0.001
Percent of positive cores (N = 350)	32% ± 23%	26% ± 20%	0.018
Maximum cancer percent (N = 454)	32% ± 25%	27% ± 24$%	0.045

metastasis; however, there is the competing risk of simply undergoing PLND, which increases a patient's risk for venous thromboembolism, lymphocele, as well as ureteral, vascular, or nerve injury [7].

We sought to determine if omission of PLND in patients with D'Amico low-risk prostate cancer increased the risk for biochemical recurrence (BCR), where the general practice, over time, has evolved from PLND for all patients undergoing prostatectomy, primarily during the open prostatectomy era, to omission of PLND during the laparoscopic/robotic era.

MATERIALS AND METHODS

Data elements of all patients undergoing prostatectomy at our institution have been recorded in an institutional review board-approved, prospectively maintained database. This database was queried for all patients with cT1-2a, clinical Gleason 3 + 3, and prostate-specific antigen (PSA) < 10 ng/mL who had not received any adjuvant or neoadjuvant therapy from the years 1990 to 2006. Patients who had undergone perineal prostatectomy and those for whom follow-up PSA data was not available were excluded from the cohort. The study population included 535 patients who had undergone open radical prostatectomy (ORP), laparoscopic radical prostatectomy (LRP), or robot-assisted radical prostatectomy (RARP). Patients were divided into 2 groups: 139 (26%) patients had undergone PLND (+PLND) at the time of prostatectomy and in 396 (74%) patients the PLND was omitted (–PLND). See Table 1 for cohort characteristics.

Data elements analyzed were age, race, preoperative PSA, number of cores obtained at biopsy, percentage of positive biopsy cores, clinical tumor stage, year of surgery, procedure type, pathological Gleason grade, pathologic tumor stage, presence of positive surgical margins, number of lymph nodes obtained, and biochemical recurrence (BCR), defined as PSA > 0.2 ng/mL.

Regarding statistical analysis, all variables were assessed for normality, and type 1 error rate was set at $\alpha = 0.05$. Baseline characteristics of men with +PLND and -PLND were compared using independent t tests for continuous variables and chi-squared tests for independence for categorical variables. Data for biopsied number of cores (N = 457), percent positive biopsy cores (N = 350), and maximum percent of cancer in any core (N = 454) were not available in the full study population, but we included all patients with available data on these parameters. Next, the Kaplan-Meier method was used to estimate BCR-free survival by PLND status. Survival curves were compared using the log-rank test and used to estimate 5-year BCR-free survival in each group. The univariate Cox proportional hazards analysis was applied to evaluate the association between the omission of PLND and BCR. In addition, the other demographical, clinical, and pathological variables listed in Table 1 were examined for associations with BCR. Validity of the proportional hazards assumption was assessed for each variable using log-log plots. In a final multivariate model, the effect of PLND was evaluated and adjusted for all other variables, with the exception of the number of biopsy cores, percent positive cores, and maximum percentage of cancer in any core because they did not predict BCR and were not available in the full study sample. The statistical analysis was completed by a statistician (BBG).

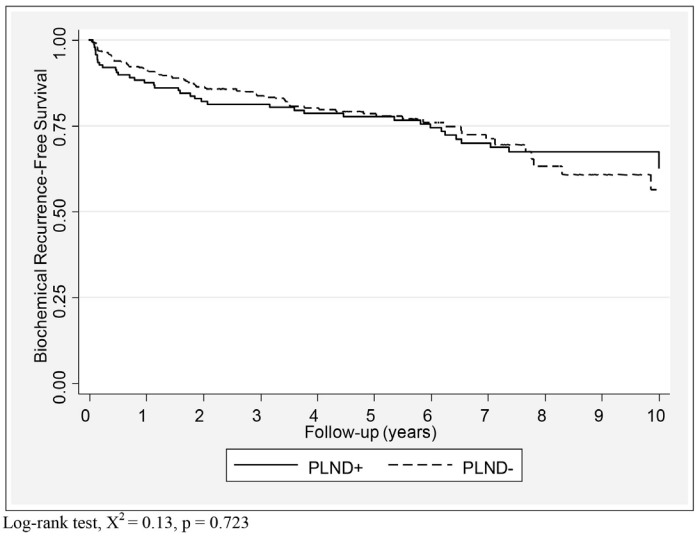
RESULTS

The median follow-up for the entire cohort was 43 months (SD 40.8 months). Men with +PLND (N = 139) and –PLND (N = 396) were similar at baseline with respect to demographics, clinical and pathological tumor stage, pathological Gleason grade, and positive margin rate (Table 1). Of note, primary pathologic Gleason 4 was diagnosed in a total of 12 of the patients (2% of the total cohort), 3 in the +PLND group, and 9 in the –PLND group. Primary pathologic Gleason 5 was diagnosed in 1 patient (0.2% of the total cohort) of the –PLND group.

Men with +PLND underwent surgery in the earlier years of the study period (P < 0.001), had a higher preoperative PSA (5.6 vs 5.1, P = 0.009), had a different distribution of prostatectomy type (more ORP, less RARP, P < 0.001), had less biopsy cores (9.4 vs 11.0, P < 0.001), a greater percentage of positive cores (32% vs 26%, P = 0.018), and a higher maximum percentage of cancer (32% vs 27%, P = 0.045).

The mean number of lymph nodes obtained at PLND was 6.2 (range 1-38). Two patients had positive nodes on pathologic analysis, both patients had 1 positive node each; both patients were pathologic Gleason 3 + 4, 1 patient was pT3a, and the other was pT3b; 1 of the patients was Caucasian, and race is not known for the other patient.

Figure 1. Biochemical recurrence-free survival by PLND group.



Log-rank test, $X^2 = 0.13$, $p = 0.723$

Kaplan-Meier BCR-free survival curves are presented in Figure 1. The curves are overlapping, suggesting similar BCR-free survival rates in both groups, which is reflected in the log-rank test (X2 = 0.13, P = 0.723). The five-year BCR-free survival rate for +PLND was 77.6% and for –PLND was 78.6%.

Univariate Cox proportional hazard ratios (HR) for BCR are reported in Table 2. –PLND did not predict BCR in unadjusted models (HR = 1.07, P = 0.723). Higher preoperative PSA, higher pathological tumor stage and Gleason score, as well as positive margins all predicted BCR. Year of surgery and type of prostatectomy also predicted BCR. Because of the numerous univariate predictors that were significantly associated with BCR, a multivariate model was completed; –PLND remained a non-significant predictor of BCR in the sample. Lastly, mean prostate volumes were statistically different at 52 mL and 45 mL for the +PLND and –PLND groups, respectively (P = 0.003), but volume was not associated with BCR (Cox HR = 1.00, P = 0.84).

DISCUSSION

Pelvic lymph node dissection has increasingly been omitted at the time of prostatectomy as the PSA era has led to a stage migration in which patients are routinely diagnosed with

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Table 2. Cox proportional hazards ratios for factors predicting biochemical recurrence.

	Univariate HR	P Value	Multivariate HR	P Value
Pelvic lyphadenectomy Yes No	 1.0 1.07	 0.723	 1.0 1.37	 0.154
Preoperative PSA (ng/mL)	1.17	0.001	1.14	0.009
Year of surgery	0.91	< 0.001	1.03	0.348
Age at surgery	1.02	0.233	1.02	0.178
Race White Black Other/unknown	 1.0 1.45 0.91	 0.062 0.836	 1.0 1.40 0.81	 0.127 0.655
Prostatectomy type RARP LRP ORP	 1.0 3.57 7.95	 0.011 < 0.001	 1.0 3.71 9.96	 0.013 < 0.001
Clinical tumor stage T1 T2	 1.0 0.64	 0.117	 1.0 0.74	 0.307
Pathological tumor stage pT1 and pT2 pT3	 1.0 2.60	 < 0.001	 1.0 1.41	 0.120
Pathological Gleason Score ≤ 3 + 3 ≥ 3 + 4	 1.0 1.75	 0.002	 1.0 1.54	 0.032
Margins Negative Positive	 1.0 3.13	 < 0.001	 1.0 2.04	 < 0.001
Number of biopsy cores (N = 437) ≤ 12 12+	 1.0 0.98	 0.469	 - 	 -
Percent positive biopsy cores (N = 350)	1.37	0.570	-	-
Maximum percent cancer in any core (N = 454)	0.99	0.883	-	-

localized prostate cancer [8]. In addition, with the introduction of nomograms, the ability to preoperatively identify those at low-risk for lymph node metastasis enabled surgeons to rationally decide in whom to omit PLND [1,2]. Currently, the most recent NCCN prostate cancer guidelines allow for exclusion of PLND in patients with < 2% predicted probability of nodal metastases by nomograms. In the absence of prospective randomized data, information from large retrospective studies provide a reasonable basis for this practice [4,5].

The results presented here, similar to the 2 studies mentioned above, support that PLND can safely be omitted in patients who are low-risk by D'Amico criteria without putting the patient at increased risk for BCR [4,5]. Our results also suggest that in this cohort of clinically low-risk patients, by omitting the PLND, the patient risk stratification would not have been obscured, as shown by examining the characteristics of the 2 patients with positive lymph nodes in the +PLND group. One patient was pT3a and the other was pT3b; therefore, both patients would have both been considered high risk for BCR just based upon the pathologic stage of the prostate gland itself, irrespective of the nodal status.

Regarding the number of cores obtained at biopsy, there was a difference between the groups; on average, 9 cores were obtained in the +PLND group and 11 total cores were obtained in the –PLND group. It could be assumed that fewer cores obtained could lead to under-detection of higher-stage or

higher-grade cancer. However, this was not the case as there was no difference between the groups on pathological staging. The percentage of positive biopsy cores was significantly higher in the +PLND group. This is likely due to the smaller denominator (positive cores/total cores) in the +PLND group, reflecting that these patients had their biopsy in the era when less total cores were obtained at the time of biopsy.

The difference in the distributions of procedure type between the –PLND and +PLND groups throughout the years of surgery reflect the change from the open to the minimally invasive approach; patients who were treated with ORP were more likely to have had PLND.

A definite strength of this study rests in the fact that the cohorts had similar preoperative and postoperative characteristics; this provides confidence in interpreting the Kaplan-Meier curve. A shortcoming of this study is the median follow-up of 43 months. However, our endpoint, BCR, most often occurs in the first 2 to 3 years following radical prostatectomy and is shown in other previously published reports [9-11]. In addition, the duration of follow-up in this study is within the range of follow-up (32-89 months) that was reported in the 2 similar, previously discussed studies [4-6].

Our study is unique in its proportion of African Americans who represented 23% of the study population. This is in contrast to other studies discussed in which African Americans represented 4.5 to 7.7% of their respective populations [4-6]. Interestingly, African American race trended toward significance as a risk factor for BCR. Whether this is related to access to care issues or actual differences in biology cannot be determined.

We do note that BCRFS in this study is lower than what would be expected for a cohort of patients with clinically low-risk disease. The above-mentioned higher proportion of African Americans in this study compared to other studies, and the fact that race showed a trend toward increasing risk for BCR, may offer an explanation.

Because smaller prostate volume has been implicated to be a risk factor for BCR, we evaluated this in our cohort [12]. While there was a statistical difference in the prostate gland volume between the groups, the Cox hazard ratio showed no association between prostate volume and BCR.

An additional limitation of this study is the limited extent of the PLND. The mean LN yield was 6, and while we do acknowledge that this represents the low end of what is reported in the literature, this may be a reflection of variability of pathological processing and reporting between institutions [13,14]. Moreover, consideration of a more extended PLND in low-risk prostate cancer patients does not appear warranted given the increased risk for adverse outcomes without proven benefit [15].

CONCLUSION

For patients with low-risk prostate cancer who have chosen to proceed with prostatectomy, a limited PLND may be omitted without compromising their BCR-free survival.

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