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Predicting Biochemical Recurrence-Free Survival in Patients With Positive Pelvic Lymph Nodes at Radical Prostatectomy

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Abstract

Purpose—We evaluated predictors of freedom from biochemical recurrence in patients with pelvic lymph node metastasis at radical prostatectomy.

Materials and Methods—Of 207 patients with lymph node metastasis treated with radical prostatectomy and bilateral pelvic lymph node dissection 45 received adjuvant androgen deprivation therapy and 162 did not. Cox proportional hazards regression models were used to investigate predictors of biochemical recurrence after radical prostatectomy. Recurrence probability was estimated using the Kaplan-Meier method.

Results—A median of 13 lymph nodes were removed. Of the patients 122 had 1, 44 had 2 and 41 had 3 or greater positive lymph nodes. Of patients without androgen deprivation therapy 103 had 1, 35 had 2 and 24 had 3 or greater positive lymph nodes while 69 experienced biochemical recurrence. Median time to recurrence in patients with 1, 2 and 3 or greater lymph nodes was 59, 13 and 3 months, respectively. Only specimen Gleason score and the number of positive lymph nodes were independent predictors of biochemical recurrence. Recurrence-free probability 2 years after prostatectomy in men without androgen deprivation with 1 positive lymph node and a prostatectomy Gleason score of 7 or less was 79% vs 29% in those with Gleason score 8 or greater and 2 or more positive lymph nodes.

Conclusions—Prognosis in patients with lymph node metastasis depends on the number of positive lymph nodes and primary tumor Gleason grade. Of all patients with lymph node metastasis 80% had 1 or 2 positive nodes. A large subset of those patients had a favorable prognosis. Full bilateral pelvic lymph node dissection should be done in patients with intermediate and high risk cancer to identify those likely to benefit from metastatic node removal.

Keywords

prostate; prostatic neoplasms; lymph node excision; neoplasm metastasis; prognosis

The role of pelvic LN dissection and treatment in patients with LN metastasis after RP remain controversial. The risk of LN metastasis in men who undergo RP for clinically localized prostate cancer is 3% to 24%.^{1–6} Patients with positive LNs at RP can have different outcomes. Some men never achieve undetectable PSA while others remain free of BCR for prolonged periods. Consequently ideal management for positive LNs at RP is

debated. Messing et al reported a survival advantage in men with LN metastasis at RP treated with immediate vs delayed ADT initiated at clinical meta-static disease.⁷ Those data support the concept that all men with positive PLND at RP should receive immediate ADT. However, some men in the delayed treatment arm never showed clinical progression or biochemical recurrence, suggesting that some with positive LNs would not benefit from immediate ADT. Reported outcomes in several large RP series suggest that up to 15% of men with positive PLND at RP remain free of BCR at 10 years.⁷⁻⁹ There are no accepted guidelines in this treatment setting.¹⁰⁻¹³ We examined a number of clinical and pathological predictors of BCR to better assess the risk of recurrence in men with positive LNs at RP.

PATIENTS AND METHODS

At our institution 4,648 patients underwent open (3,378) or laparoscopic (1,270) RP with BPLND from January 2000 to September 2008. Our standard BPLND included removal of all fibroadipose tissue in the external iliac, obturator and hypogastric fossae. Standard BPLND was routine in patients undergoing open RP during this time and in those undergoing laparoscopic RP after February 1, 2003 (893). Only patients with a standard BPLND were included in analysis. A total of 57 patients with open and 388 with laparoscopic surgery had no PLND or underwent more limited dissection and were excluded from analysis.

In all treated patients RP was done contemporaneously with our study. Frozen sections were not routinely used. All RP specimens were serially sectioned at 3 to 5 mm, entirely submitted for permanent section and examined on whole mount slides. All LN specimens were sent en bloc for permanent section pathological analysis. After fixation in 10% neutral buffered formalin the LNs were meticulously dissected and counted manually by the pathologists. Each identified LN was cut when appropriate, embedded in paraffin, sectioned at 5 μ m, stained with hematoxylin and eosin, and examined microscopically. No immunohistochemical staining for keratin or PSA and no reverse transcriptase-polymerase chain reaction technology was used. Residual adipose tissue from lymphadenectomy specimens was preserved in the specimen container in formalin until the surgical pathology case was signed out and then discarded according to College of American Pathologists guidelines. BCR was defined as PSA 0.1 ng/ml or greater with 1 confirmatory increase.¹⁴ ADT was discussed with the patient and individually administered at treating physician discretion. Patients were followed with physical examination and PSA measurement every 3 months during year 1 after surgery, every 6 months during years 2 and 3, and annually thereafter.

We identified 224 patients (5.3%) with positive LNs of those who underwent BPLND. Excluded from study were 11 patients with any neoadjuvant therapy, 4 with adjuvant radiotherapy or chemotherapy and 2 lost to followup. Thus, the final cohort for analysis included 207 patients, including 170 with open and 37 with laparoscopic RP, of whom 45 (22%) received adjuvant ADT and 162 (78%) did not. Median followup for survivors was 30 months with 39 (almost 20%) of the 207 alive and followed for more than 5 years after surgery.

Statistical Methods

Univariate and multivariate Cox proportional hazards regression models were used to investigate predictors of BCR after RP. Analysis was restricted to the 162 patients without adjuvant ADT since we intended to investigate factors associated with freedom from recurrence in an untreated group, so that these results could possibly inform the decision to provide adjuvant treatment. Predictors analyzed were pretreatment PSA, pathology Gleason

grade, extracapsular extension, seminal vesicle invasion and number of positive LNs. All pathological parameters were obtained from pathology reports. PSA was analyzed as a continuous variable with log transformation. Pathological Gleason grade was categorized as 7 or less and 8 or greater. Gleason 6 or less was combined with Gleason 7 because few patients had pathological Gleason grade 6 or less. The number of positive LNs was categorized as 1, 2 and 3 or greater. All predictors were prespecified before data analysis and included in the multivariate model. Recurrence probability was estimated using the Kaplan-Meier method in patients without adjuvant therapy. Statistical analysis was done using Stata® 10.1.

RESULTS

In the cohort of 207 patients with positive LNs a median of 13 LNs (IQR 9–19, range 2 to 48) were removed. When stratifying this cohort into 162 men without and 45 with adjuvant ADT a median of 14 (IQR 9–20, range 2 to 48) and 11 LNs (IQR 8–17, range 3 to 32) were removed, respectively. Of the 207 patients 122 (59%) had only 1, 44 (21%) had 2 and 41 (20%) had 3 or more positive LNs. The highest number of positive LNs in an individual was 18. Table 1 lists patient characteristics in the total cohort and separately in those with and without adjuvant ADT. Patients with adjuvant ADT had higher pathology Gleason scores in the RP specimen (grade 8 or greater in 67% vs 49%) and a greater number of positive LNs (3 or more in 38% vs 15%).

Of the 162 patients without adjuvant ADT 103 (64%) had 1, 35 (22%) had 2 and 24 (15%) had 3 or more positive nodes. A total of 69 men experienced BCR with a 19-month median followup in BCR-free patients. Overall the 24-month probability of freedom from BCR was 55% (95% CI 46–63, part A of sole figure). Median time to recurrence in patients with 1, 2 and 3 or more positive LNs was 59, 13 and 3 months, respectively.

On univariate analysis higher pre-RP PSA, RP Gleason score, seminal vesical invasion and number of positive LNs were significantly associated with BCR (each $p < 0.01$, table 2). On multivariate analysis only RP Gleason score (8 or greater vs 7 or less HR 2.04, 95% CI 1.15–3.64) and number of positive LNs (2 vs 1 HR 1.16, 95% CI 0.57–2.35 and 3 or greater vs 1 HR 3.11, 95% CI 1.57–6.16) were independent predictors of BCR (table 2). Parts B and C of the sole figure show Kaplan-Meier recurrence-free probability stratified by the number of positive nodes and by RP Gleason score, respectively. After RP 24-month recurrence-free probability in men with 1, 2 and 3 or greater positive LNs was 65% (95% CI 54–74), 48% (95% CI 29–65) and 10% (95% CI 1–35), respectively. Patients with an RP Gleason score of 7 or less had a 72% (95% CI 60–81) recurrence-free probability at 24 months vs 36% (95% CI 23–48) in those with a specimen Gleason sum of 8 or greater. The most favorable group with an RP Gleason score of 7 or less and only 1 positive LN, comprising 38% of the men without ADT, had a 79% likelihood (95% CI 65–87) of remaining free from BCR 2 years after RP (table 3). In the total cohort with positive LNs with and without ADT the group with a single positive LN and Gleason score 7 or less, comprising 34% of all patients, had a 74% likelihood of remaining free of BCR 2 years after RP (table 2).

DISCUSSION

Several studies show that a greater number of LNs removed is associated with an increased probability of detecting and removing a positive LN.^{4,10,15–18} Sparing the internal iliac LNs from BPLND, as done in limited LND, would lead to almost 20% of LN positive cases not being identified.⁵ Comparable to the anatomical yield of standard BPLND in our study cohort, Bader et al reported a 25% LN metastasis rate in patients undergoing meticulous lymph node dissection.¹² Of these 92 patients with positive LNs 39 (42%) had only 1

positive LN, of whom 15 (38%) remained free of BCR at a median 45-month followup. Meticulous LN dissection in our study, including the removal of all fibroadipose tissue in the external iliac, obturator and hypogastric fossae, showed that 80% of all LN positive cases had only 1 or 2 positive LNs. Allaf et al reported a greater proportion of occult metastasis identified in men diagnosed with prostate cancer who underwent extended rather than limited BPLND.⁴ Based on these data they concluded that patients with a minimal nodal burden may be the subpopulation that may benefit the most from extended BPLND. Our data and that in other studies^{4,16,19,20} show that most patients with prostate cancer with lymph node metastasis have only 1 or 2 positive LNs. A subgroup of these men, especially those with Gleason grade 7 or less in the primary tumor, seem to benefit the most from removing LN metastasis. Hence, complete BPLND should be done to provide optimal staging and the best therapeutic outcome in all patients with prostate cancer at intermediate and high risk.

The role of immediate adjuvant therapy in men with positive LNs at RP is controversial. The strongest evidence in favor of adjuvant ADT in this setting comes from the studies by Messing et al, who observed prostate cancer specific and overall survival advantages in favor of immediate adjuvant ADT.^{7,21} The main criticisms of this study are based on the lack of a standardized template for PLND (some men underwent only limited dissection), late ADT in men randomized to the deferred treatment group (ADT initiation at clinical rather than biochemical failure) and the small sample size. However, other investigators noted no difference in outcome between early vs deferred ADT in men with positive LNs. Schroder et al reported results in patients in European Organisation for Research and Treatment of Cancer Protocol 30846 with locally confined or locally advanced prostate cancer and histologically or cytologically confirmed LN metastasis who were randomized to early or deferred ADT.²² In contrast to the trial by Messing et al,²¹ men in the former study did not receive prior treatment other than LN dissection or LN biopsy.²² At a median 13-year followup similar cancer specific and overall survival was seen in the groups. Two questions arise regarding men with positive LNs at RP. 1) Do all such men require immediate ADT? 2) Are there predictors that may allow the selection of those at low risk for early BCR in whom systemic therapy may be delayed? For question 1 several investigators observed that not all men with positive LNs are destined for early biochemical failure and some never experience failure.^{10,12,13} Immediate ADT in these men would provide no benefit and subject them to the negative aspects of long-term ADT.

Our intent was to address the second question, that is which clinical and pathological factors are associated with freedom from BCR in men with positive LNs undergoing RP plus BPLND who did not receive ADT? In our analysis RP Gleason score and number of positive LNs were independent predictors of BCR. Results support the conclusions of others that patients with a higher number of positive LNs are at increased risk for BCR and cancer specific death.^{12,23} Palapattu et al retrospectively reviewed the records of 3,264 patients treated with RP and PLND, of whom 143 had LN involvement.¹³ Similar to our findings, they observed that higher Gleason score and greater LN burden were associated with worse prognosis and increased BCR risk.¹³ Fleischmann et al retrospectively evaluated histopathological risk factors in a cohort of 102 patients with positive LNs at RP.²³ They suggested that involved LN diameter (10 or less vs greater than 10 mm) and “micrometastasis only status” were significantly associated with the likelihood of BCR. Stratifying our patients into subgroups based on the number of positive LNs and specimen Gleason score showed a remarkable difference in recurrence-free probability. The risk associated with BCR was approximately 3 times higher in men with 3 or more vs 1 positive LN and approximately 2 times higher in those with pathology Gleason 8 or higher vs 7 or less. Our lowest risk group with 1 positive LN and RP Gleason score 7 or less, representing 38% of our population of men with positive LNs without immediate ADT, did remarkably

well with a 79% probability of freedom from BCR at 24 months. They may benefit from an observation period rather than immediate systemic therapy.

The limitations of our study are those associated with its retrospective design. This is a single institution study with limited followup. In our analysis we did not include potential prognostic factors, such as size of the metastatic deposit in the LN. All patients underwent such thorough LN dissection that our results may not be generalizable to those with more limited dissection. Study strengths are the prospective followup and standardization of the BPLND done in all patients. The optimal timing of systemic therapy in patients with positive LNs at RP remains open but some observations deserve attention. Most patients with LN metastasis do have only 1 or 2 positive LNs in the dissected yield described previously and may benefit the most from thorough, full BPLND. Not all patients with a positive LN at RP experience BCR. Even in those in whom BCR develops several years may pass after RP before BCR is detected. Thus, it seems rational that men with positive LNs at RP be risk stratified. Those at low risk for early BCR may be suitable candidates for observation strategies while those at higher risk may benefit from adjuvant ADT or be selected for clinical trial participation. Stratification can be guided by RP Gleason score and the number of positive LNs.

CONCLUSIONS

Prognosis in patients with LN metastasis depends on the number of positive LNs removed and primary tumor Gleason grade. Despite a median of 13 LNs removed 80% of all patients with LN metastasis had only 1 or 2 positive LNs. A surprisingly large subset of LN positive cases with 1 positive LN and Gleason score 7 or less had a favorable prognosis. Full BPLND should be done in patients with intermediate and high risk cancer to optimally identify those with a minimal LN burden who may benefit the most from metastatic LN removal. Patients with RP Gleason score 8 or higher and 2 or more positive LNs are at an increased risk for BCR and should be considered candidates for adjuvant ADT or for enrollment in clinical trials to further investigate adjuvant therapy.

Abbreviations and Acronyms

ADT	androgen deprivation therapy
BCR	biochemical recurrence
BPLND	bilateral PLND
LN	lymph node
PLND	pelvic LN dissection
PSA	prostate specific antigen
RP	radical prostatectomy

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Figure 1. Kaplan-Meier estimated BCR freedom in men with positive LNs *A*, no ADT. *B*, no ADT stratified by number of positive LNs. *C*, no ADT stratified by pathology Gleason grade.

Table 1

Patient characteristics in total cohort and stratified by those with vs without ADT

	No. Pts	No ADT	ADT	Overall
Median age at surgery (IQR)	60	(56–65)	62	(55–66)
Median ng/ml pretreatment PSA (IQR)	206	8.11 (5.30–13.5)	8.68 (5.35–13.4)	8.21 (5.30–13.4)
No. biopsy Gleason score (%):	202			
6 or Less	34	(22)	5	(11)
7	67	(42)	21	(48)
8 or Greater	57	(36)	18	(41)
No. clinical stage (%):	195			
T1C or less	47	(31)	8	(20)
T2A	32	(21)	8	(20)
T2B	54	(35)	8	(20)
T3/4	21	(14)	17	(41)
No. pathology Gleason score (%):	203			
6 or Less	3	(2)	0	(3)
7	79	(49)	14	(33)
8 or Greater	78	(49)	29	(67)
No. pathological stage (%):	200			
pT2	26	(16)	3	(7)
pT3a	71	(44)	18	(43)
pT3b or Greater	61	(39)	21	(50)
No. extracapsular extension (%)	201	(82)	38	(90)
No. seminal vesicle invasion (%)	200	(39)	21	(50)
No. pos surgical margin (%)	200	(33)	19	(45)
Median No. LN removed (IQR)	14	(9–20)	11	(8–17)
No. pos LN (%):				
1	103	(64)	19	(42)
2	35	(22)	9	(20)
3 or Greater	24	(15)	17	(38)

Table 2

Univariate and multivariate Cox regression of BCR predictors in men with positive LNs

Predictor	Univariate		Multivariate	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Log PSA	1.64 (1.19–2.25)	0.002	1.29 (0.91–1.82)	0.15
Pathology Gleason 8 or greater vs 7 or less	2.87 (1.71–4.79)	<0.001	2.04 (1.15–3.64)	0.015
Extracapsular extension (yes vs no)	1.28 (0.66–2.52)	0.5	0.84 (0.39–1.79)	0.6
Seminal vesicle invasion (yes vs no)	2.25 (1.38–3.66)	0.001	1.43 (0.80–2.54)	0.2
No. pos LNs:		<0.001		0.003
2 vs 1	1.74 (0.94–3.20)		1.16 (0.57–2.35)	
3 or Greater vs 1	5.14 (2.84–9.34)		3.11 (1.57–6.16)	

Table 3

Two-year BCR-free probability in men without ADT and overall by number of positive LNs and Gleason score

Gleason Score	1 Pos LN	2 or Greater Pos LNs
<i>No ADT</i>		
7 or Less:		
No. pts (%)	61 (38)	21 (13)
Median % BCR free (95% CI)	79 (65–87)	46 (18–70)
8 or Greater:		
No. pts (%)	41 (26)	37 (23)
Median % BCR free (95% CI)	40 (21–59)	29 (14–45)
<i>Overall</i>		
7 or Less:		
No. pts (%)	70 (34)	26 (13)
Median % BCR free (95% CI)	74 (61–83)	52 (26–73)
8 or Greater:		
No. pts (%)	51 (25)	56 (28)
Median % BCR free (95% CI)	42 (26–58)	32 (19–45)