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PROGNOSTIC FACTORS IN LYMPH NODE-POSITIVE PROSTATE CANCER

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ABSTRACT

Objectives. To characterize lymph node metastasis of prostate cancer (PCa) and identify the parameters associated with patient outcome. The incidence of clinically localized PCa with concurrent lymph node metastasis has decreased to less than 1% in the United States but is between 10% and 15% in other countries.

Methods. Our study cohort of 1148 patients underwent radical prostatectomy in Ulm, Germany, between 1986 and 2002, and 201 (18%) had lymph node-positive PCa.

Results. The metastases showed growth architecture resembling primary PCa. We assigned a Gleason pattern and evaluated for size, extranodal extension, and lymphovascular invasion (LVI). Of 201 patients, 155 had original pathology slides available; 36 of the 155 were excluded because of preoperative hormonal ablation therapy. Of the remaining 119 patients, 22 (19%) were assigned Gleason pattern 3, 93 (78%) Gleason pattern 4, and 4 (3%) Gleason pattern 5. Extranodal extension was present in 66 (55%) of 119 patients and LVI in 29 (25%). An increased risk of prostate-specific antigen (PSA) recurrence was found for Gleason pattern 4/5 (hazard ratio [HR] 2.5, $P = 0.038$), LVI in the lymph nodes (HR 1.9, $P = 0.038$), and nuclear grade of the primary tumor (HR 2, $P = 0.025$). Independent predictors of PSA recurrence included LVI and nuclear grade (HR 1.9, $P = 0.03$ and HR 2, $P = 0.03$, respectively).

Conclusions. Lymph node metastases of PCa are heterogeneous and have a close relation to the corresponding primary tumor. Most patients with lymph node-positive PCa remained disease free for up to 13 years after radical prostatectomy. Independent predictors of PSA recurrence among those with lymph node-positive PCa included LVI in the lymph nodes and the nuclear grade of the primary tumor. These parameters may be useful in predicting PSA recurrence in lymph node-positive PCa and could be included in patient follow-up. UROLOGY **67:** 1016–1021, 2006. © 2006 Elsevier Inc.

The presence of prostate cancer (PCa) lymph node metastasis is rarely seen in regions with prevalent prostate-specific antigen (PSA) screening; however, among unscreened populations, lymph node metastasis is not uncommon.[1] Previous studies have indicated the long-term survival of men with PCa involvement of the pelvic lymph nodes removed during radical prostatectomy,[2,3] suggesting that radical prostatectomy may have a role in the management of locally advanced PCa. Nevertheless, some urologists abort prostatectomy if lymph node metastasis is detected on frozen section analysis. Additional characterization of the prognosis for patients with lymph node-positive PCa may help reconcile these divergent management approaches of aggressive resection versus aborted prostatectomy in such cases.

Earlier reports showed that the number of positive lymph nodes and the lymph node tumor burden were independently associated with disease

This study was supported by a Department of Defense Fellowship Award PC030214 to M. D. Hofer, a Career Development Award from the Dana-Farber/Harvard Cancer Center Specialized Program of Research Excellence (SPORE) for Prostate Cancer to M. D. Hofer, and National Cancer Institute grants P50CA90381 and R01AG21404 to M. A. Rubin.

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Submitted: August 20, 2005, accepted (with revisions): October 31, 2005

0090-4295/06/$32.00
doi:10.1016/j.urology.2005.10.055

progression, suggesting that patient prognosis could be assessed from these pathologic parameters.[1,3,4] One limitation to using these parameters is that they cannot be easily assessed during routine intraoperative or postoperative pathologic examination. In the present study, we analyzed a cohort of 201 patients with PCa involving the pelvic lymph nodes to identify the prognostic parameters of such PCa cases and to explore the biologic relationship of lymph node metastases with respect to the primary tumor.

MATERIAL AND METHODS

Patient Population

A total of 1118 men diagnosed with clinically localized and locally advanced PCa, who underwent radical prostatectomy and pelvic lymph node dissection with curative intent at the University of Ulm Hospital (Ulm, Germany) as standardized in our institution between 1986 and 2002, were considered for inclusion in this study. The internal review board approved the study before the patients were enrolled. All tumors were restaged using the 2002 TNM system[5,6] and graded according to the system originally described by Gleason.[7,8] The PSA level was measured before surgery and was not part of a systematic screening regimen. Of the 1118 patients, 201 (18%) had lymph node-positive disease. All patients underwent androgen ablation therapy postoperatively. The original pathology slides were retrieved for 155 patients, of whom 36 patients were excluded because they had undergone preoperative hormonal ablation therapy. Although no established protocol has been developed for grading positive lymph nodes, for the purposes of generating a hypothesis, the metastatic tumors were graded on the basis of the architectural growth, using similar guidelines as described by Gleason for clinically localized PCa.

PSA failure was defined as an increase in the postoperative serum PSA level to greater than 0.4 ng/mL on two consecutive measurements, with the earlier date defined as the date of failure. Serum PSA levels were taken every 6 months during follow-up in the first 2 years and at least annually afterward. The assay types varied during the years of this study and did not conform to a specific protocol.

Pathologic Examination

Morphometric analysis was performed by the study pathologists (W.H., T.A.B., M.A.R.). Serial sections of each lymph node were analyzed. The tumor burden was estimated by multiplying the length and width of the metastases. The number of metastatic foci was obtained by counting the separate foci in all the lymph nodes of each patient. Extranodal extension was present if the tumor had expanded beyond the lymph node capsule in the perinodal fatty tissue. Lymphovascular invasion (LVI) was considered present when tumor cells were found within the lumen of the blood vessels and/or nodal sinuses. The nuclear grade of the primary tumor (according to World Health Organization guidelines) and the number of dissected and positive lymph nodes were obtained from the original pathology reports.

Statistical Analysis

Cox proportional hazard regression analysis was used for univariate and multivariate analyses of continuous and categorical data of the clinical and pathologic parameters. A backward selection procedure with a cutoff level of 0.15 was used to choose the most parsimonious model in predicting PSA-free survival. Statistical analyses were performed using Statistical Analysis System (SAS Institute, Cary, NC) and the Statistical Package for Social Sciences (SPSS, Chicago, Ill), with a significance level of 0.05.

TABLE I. *Characteristics of patients with lymph node-positive prostate cancer (n = 201)*

Characteristic	n (%)
LN involved	
1	88 (44)
2	45 (22)
>2	68 (34)
T stage	
2	10 (5)
3	37 (18)
3a	16 (8)
3b	45 (22)
3c	57 (28)
4	36 (18)
PSA failure*	83 (41)
Mean No. of removed lymph nodes	12 (1–46)
Mean No. of positive lymph nodes	3 (1–15)
Mean preoperative PSA (ng/mL)	37 (0.2–310.0)
Mean age at operation (yr)	64 (48–78)

Key: LN = lymph node; PSA = prostate-specific antigen.
Data in parentheses are ranges, unless otherwise noted.
** PSA >0.4 ng/mL.*

RESULTS

Demographics of Patients with Lymph Node-Positive PCa

The patient demographics for the 201 patients with lymph node-positive PCa are presented in Table I. The mean number of dissected lymph nodes at radical prostatectomy was 12, and the mean number of positive lymph nodes was 3. Almost 50% of patients had only one, 22% had two, and 34% had more than two positive lymph nodes. PSA failure occurred in 41% of patients with lymph node-positive PCa, and 59% were disease free after a mean follow-up of 41 months (range 1 to 151). The 5-year PSA failure-free survival rate was 61%, and the mean PSA failure-free survival time was 54 months.

Morphologic Features of Pelvic Lymph Node-Positive PCa Associated with PSA Recurrence Risk

We analyzed the metastases of the 119 patients who fulfilled our inclusion criteria. Two attributes of lymph node metastasis were readily apparent. First, the number of metastatic lymph nodes was not associated with the total tumor burden among all the metastases of an individual patient. Instead, patients with only one positive node often had a larger metastatic burden than patients with more positive nodes (Fig. 1A). Second, the metastatic growth pattern observed in the 119 patients was similar to the architectural growth pattern used for

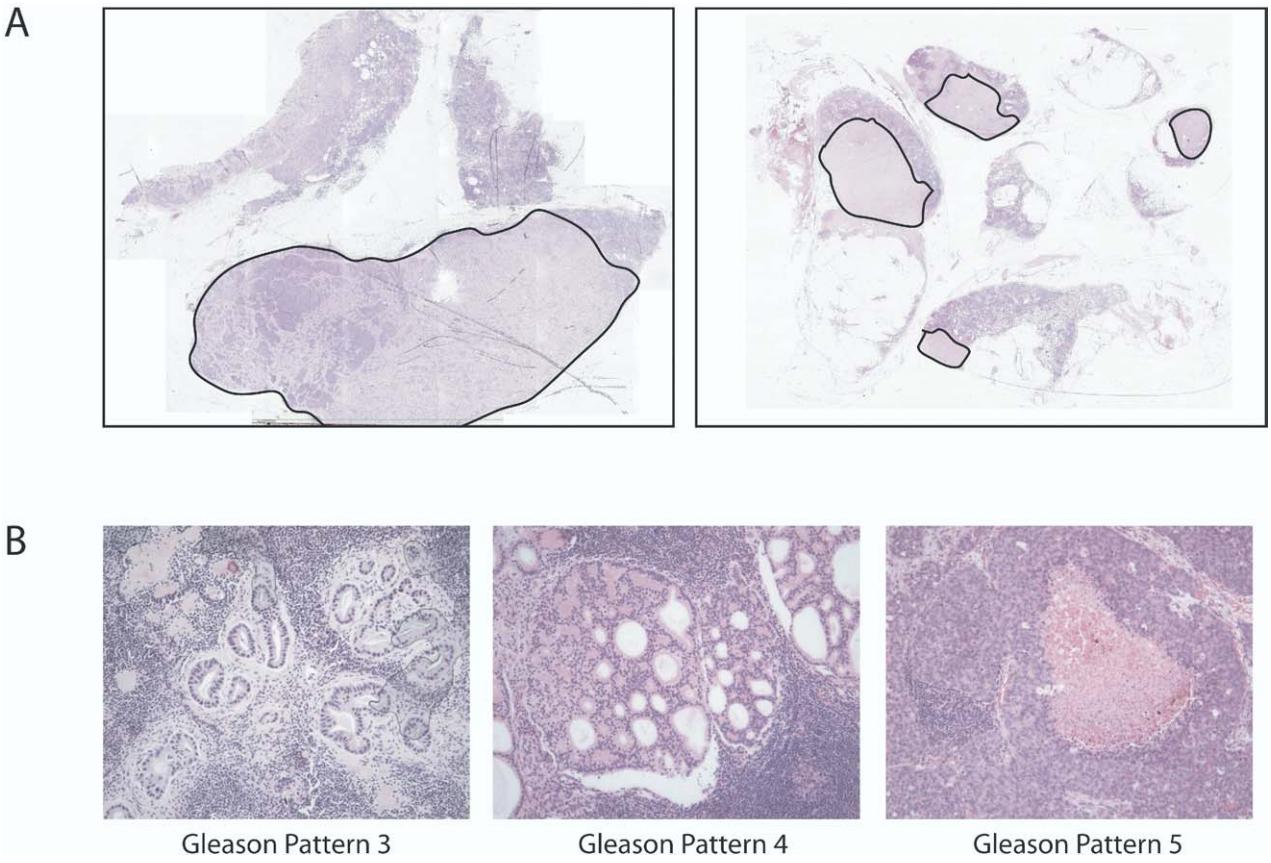

FIGURE 1. *(A) Variable lymph node involvement by metastatic PCa best observed by examining lymph nodes at low magnification (2×); circled areas indicate metastatic tumor. Total tumor burden was not associated with number of positive lymph nodes. (Left) Only one node involved but tumor bulk greater than that (Right) in patient with four positive lymph nodes. (B) Glandular architecture of metastatic lymph nodes assessed for 155 cases using similar guidelines as described by Gleason. Some metastatic tumors had low-grade growth (similar to Gleason pattern 3), and others had high-grade growth, similar to Gleason pattern 4 or, when necrosis was seen, grade 5.*

grading the primary PCa, as originally described by Gleason.[7,8] We, therefore, assigned a Gleason pattern to each lymph node metastasis. Because the growth architecture within the metastases of one PCa was homogeneous, the assignment of a secondary (minor) Gleason pattern was not warranted. Generally, the Gleason pattern in the lymph nodes of an individual patient showed the same Gleason pattern. The patterns observed were indistinguishable from those seen in the primary tumor of the prostate (Fig. 1B). We observed a well-differentiated appearance similar to Gleason pattern 3 (19% of cases, Table II), cribriform growth similar to Gleason pattern 4 (78%), and solid sheets, cords, or single cells with or without central comedonecrosis similar to Gleason pattern 5 (3%). The Gleason pattern in the metastases correlated significantly with the Gleason score and nuclear grade of the primary tumor (Pearson's correlation $r = 0.4$, $P = 0.002$ and $r = 0.2$, $P = 0.022$, respectively) and with the tumor burden in the metastases ($r = 0.39$, $P < 0.0001$). Extranodal extension was seen in 66 (55%) of 119 patients, and 29 (25%) of 119 patients had lymph nodes with signs of LVI. The presence of both parameters correlated significantly with the other ($r = 0.22$, $P = 0.017$).

We explored whether these parameters were associated with PCa progression, as determined by PSA progression. The standard practice in this cohort was that patients with lymph node involvement at prostatectomy underwent adjuvant hormonal ablation therapy (as supported by more recent randomized trial data[10]). In this context of consistent adjuvant hormonal therapy, we used PSA recurrence as a surrogate for PCa progression. Of the 119 patients, 51 (43%) had developed PSA failure as of December 2003 (mean follow-up for this subgroup of patients 39 months, range 1 to 151). We had observed a wide range of preoperative PSA levels (0.2 to 310 ng/mL), with the greatest levels confounded by the presence of prostatitis reported by the pathologist. The preoperative PSA levels were not significantly associated with PSA failure or the time to postoperative PSA recurrence in this high-risk cohort.

At the univariate level, the nuclear grade of the primary tumor and LVI in the metastases were significantly associated with PSA recurrence (Table III).

TABLE II. *Histopathologic characteristics of prostate cancer lymph node metastases (n = 110–119*)*

Characteristic	n (%)
PSA failure	
Yes	68 (57)
No	51 (43)
Lymphovascular invasion	29 (25)
Gleason pattern	
3	22 (19)
4	93 (78)
5	4 (3)
Extranodal extension	66 (56)
Nuclear grade of primary*	
I	2 (2)
II	43 (40)
III	65 (59)
Area of metastasis (mm^2)	
Range	1–1439
Mean	63
Median	20

KEY: PSA = prostate-specific antigen.
** Nuclear grade could only be retrieved for 110 patients from original pathology reports; number of patients for all other entries = 119.*

TABLE III. *Regression analysis of pathologic parameters associated with PSA recurrence in men with LN+ prostate cancer (n = 119)*

Analysis	Hazard Ratio	95% CI	*P* Value
Univariate			
Lymphovascular invasion	1.9	1–3.3	0.038*
Gleason grade			
3 (Ref)	1 (Ref)		
4/5	2.5	1.1–5.9	0.038*
Extranodal extension	1.6	0.9–2.8	0.122
Area of metastasis	1	0.99–1	0.527
Nuclear grade			
G1/G2 (n = 55)	1 (Ref)		
G3/G4 (n = 77)	2	1.1–3.8	0.025*
T stage			
T2/T3 (n = 119)	1 (Ref)		
T4 (n = 17)	1.7	0.8–3.6	0.17
Multivariate			
Gleason grade 4/5	2.1	0.9–5	0.1
Lymphovascular invasion	1.9	1.1–3.5	0.03*
Nuclear grade III	2	1.1–3.6	0.03*

KEY: PSA = prostate-specific antigen; LN+ = lymph node positive; CI = confidence interval; Ref = reference.
** These parameters were significant with P <0.05.*

As in the primary tumors, Gleason pattern 4 and 5 (versus 3) in the lymph nodes was also significantly associated with an increased risk of PSA failure and was the strongest predictor. On multivariate analyses, the final model included Gleason pattern and LVI of the metastases and nuclear tumor grade of the primary PCa (Table III). Only LVI of the lymph nodes and nuclear grade of the primary were significantly associated with PSA recurrence.

COMMENT

PCa metastatic to the lymph nodes is rarely seen in the United States, mainly because of intensified PSA screening. Recent prostatectomy series in PSA-screened populations have suggested that the incidence of lymph node-positive PCa is between 4% to 6% in men undergoing surgery for presumed clinically localized PCa.[11,12] Lymph node involvement of PCa is more common among populations at the many sites worldwide where PSA screening is not included in clinical practice. Bader *et al.*[1] found lymph node metastases in 25% of patients in a PSA underscreened population. If advanced disease cannot be entirely excluded preoperatively, pelvic lymphadenectomy and frozen section analysis are performed before prostatectomy. In some settings, surgery is abrogated if metastases are found. However, it has been previously noted that patients with lymph node-positive PCa may benefit from surgery,[10,13,14] suggesting that radical prostatectomy in the setting of positive pelvic lymph nodes may still be beneficial in controlling locally advanced disease. In the present study, we determined the overall postoperative prognosis of patients with lymph node-positive PCa, evaluated the biologic relationship of lymph node metastases with respect to the primary tumor, and analyzed which histopathologic parameters may contribute in the risk assessment for PSA recurrence as a surrogate parameter for postoperative disease progression.

We found that 59% of patients with lymph node-positive PCa remained free of disease recurrence for up to 13 years after radical prostatectomy, consistent with prior reports.[10,13,14] PSA recurrence is an indicator of the presence of residual cancer or micrometastases,[10,15,16] and we used PSA recurrence as a surrogate parameter for disease progression, because the number of patients who died of PCa was too small.

We discovered a wide variation in the number of positive lymph nodes, number of metastatic foci within lymph nodes, and tumor burden among these patients. One observation was that the differentiated growth of the metastases resembled the growth patterns of the primary PCa, as described by Gleason.[7,8] In general, lymph node metastases in separate nodes in an individual patient were identical with regard to the Gleason pattern or other pathologic parameters. The Gleason pattern correlated significantly with the Gleason score and nuclear

grade of the primary PCa, with both parameters serving as a marker for tumor differentiation. Our results suggest that differentiation is a significant parameter of PCa progression and that PCa can maintain its growth characteristics when metastasizing to lymph nodes for a considerable time before undergoing additional dedifferentiation. This may contribute to long-term survival in patients with lymph node-positive PCa. Similar growth patterns can still be recognized in hormone-refractory metastases.[9] Previous studies have attempted to grade PCa metastases[17–20] and have described an association between tumor differentiation and disease progression. These studies differed from ours because they used grading systems that have been replaced by the Gleason grade[18–20] or their patient cohorts were less characteristic of today's clinical setting. For example, Cheng *et al.*[21] reviewed lymph node-positive cases obtained from 1987 to 1992. In contrast, 87% of our patients underwent surgery after 1992, a time in which development of PSA screening (even if lower than in the United States), increased awareness of PCa, and extended biopsy regimens contributed to earlier detection.

Cheng *et al.*[3] had previously demonstrated that a single positive lymph node placed a patient at a 1.5-times greater risk of dying of PCa compared with patients with lymph node-negative disease. However, no difference in disease progression was observed between patients with one or more than one positive lymph node. This suggests that the number of positive lymph nodes and the derivatives of this parameter such as lymph node density are not the most reliable predictor of patient outcome. One possible explanation is that the lymph node tumor burden is often not associated with the number of positive nodes, as we demonstrated in the present study. The Gleason pattern, LVI in the nodes, and nuclear grade of the primary tumor seemed to have greater effect on outcome.

We observed a great heterogeneity of lymph node-positive PCa, as expressed by the range of Gleason patterns, the number of dissected and positive lymph nodes, and the preoperative PSA level. Therefore, not all of our conclusions should be extrapolated to an individual case but should be seen in the context of this cohort of patients with high-risk PCa.

CONCLUSIONS

Although the Gleason pattern of the lymph nodes, along with LVI and the nuclear grade of the primary tumor, was significantly associated with PSA recurrence, the independent predictors of disease progression included only LVI and the nuclear grade of the primary tumor. A prospective study that includes histopathologic parameters such as Gleason pattern, LVI, and extranodal extension could evaluate the benefit of these parameters in the risk assessment of patients with lymph node-positive PCa. This could be useful for tailoring a follow-up regimen and for considering adjuvant therapy in addition to hormonal ablation.

ACKNOWLEDGMENT. To James E. Montie for providing the University of Michigan radical prostatectomy data.

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