Pathological Features of Lymph Node Metastasis for Predicting Biochemical Recurrence After Radical Prostatectomy for Prostate Cancer

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Abbreviations and Acronyms

BCR = biochemical recurrence
ENE = extranodal extension
EPE = extraprostatic extension
LN = lymph node
LND = LN density
LNM = LN metastasis
PLND = pelvic LN dissection
PSA = prostate specific antigen
RP = radical prostatectomy
SVI = seminal vesicle invasion

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Purpose: Subclassification of nodal stage may have prognostic value in men with lymph node metastasis at radical prostatectomy. We explored the role of extranodal extension, size of the largest metastatic lymph node and the largest metastasis, and lymph node density as predictors of biochemical recurrence.

Materials and Methods: We reviewed pathological material from 261 patients with node positive prostate cancer. We examined the predictive value when adding the additional pathology findings to a base model including extraprostatic extension, seminal vesicle invasion, radical prostatectomy Gleason score, prostate specific antigen and number of positive lymph nodes using the Cox proportional hazards regression and Harrell concordance index.

Results: The median number of lymph nodes removed was 14 (IQR 9, 20) and the median number of positive lymph nodes was 1 (IQR 1, 2). At a median followup of 4.6 years (IQR 3.2, 6.0) 155 of 261 patients experienced biochemical recurrence. The mean 5-year biochemical recurrence-free survival rate was 39% (95% CI 33–46). Median diameter of the largest metastatic lymph node was 9 mm (IQR 5, 16). On Cox regression radical prostatectomy specimen Gleason score (greater than 7 vs 7 or less), number of positive lymph nodes (3 or greater vs 1 or 2), seminal vesicle invasion and prostate specific antigen were associated with significantly increased risks of biochemical recurrence. On subset analysis metastasis size significantly improved model discrimination (base model Harrell concordance index 0.700 vs 0.655, $p = 0.032$).

Conclusions: Our study confirms that the number of positive lymph nodes is a predictor of biochemical recurrence in men with node positive disease. The improvement in prognostic value of measuring the metastatic focus warrants further investigation.

Key Words: prostate, prostatic neoplasms, lymph node dissection, neoplasm recurrence, prognosis

ACCURATE LN staging is important for prostate cancer management. It allows for reliably predicting prognosis and planning adjuvant therapy.[1] The 1992 TNM classification included a subclassification for node positive disease based on the size of a single LN (N1—metastasis in a single node 20 mm or less in greatest dimension, N2—greatest dimension 20 to 50 mm

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or multiple nodes and N3—greatest dimension greater than 50 mm). However, the clinical and pathological version of the 2010 TNM revision does not substratify LNM and it involves only 3 categories, including NX—regional LNs not assessed/sampled, N0—no positive/regional LNM and N1—metastasis in regional LN(s).[1]

Some groups investigating prognostic factors that influence prostate cancer outcomes in patients with LNM suggested including the number of positive LNs, size of the largest metastasis and the presence of micrometastasis in pN substaging.[1–4] While the role of the number of positive LNs and LND as prognostic factors is well accepted,[2,5,6] data on ENE, positive LN size and size of the metastatic focus in the LN remain controversial and have been under studied.[1,3,7,8]

We examined the prognostic role of detailed histopathological variables, such as ENE, size of the metastatic LN and of the metastatic focus in the LN, and LND in men with node positive prostate cancer treated with RP without adjuvant hormonal therapy.

METHODS

This study is an institutional review board approved analysis of data on patients treated for prostate cancer with RP plus PLND by 1 of 15 surgeons at our institution between January 2000 and December 2008. During this period 5,208 patients underwent RP plus PLND, of whom 296 were LN positive. The 21 patients treated with salvage RP were excluded, as were those with missing pathological data (Gleason score in 8, EPE in 2 and SVI in 4), leaving 261 available for analysis. Standard PLND at our institution included removal of the external iliac, obturator and hypogastric LN packets.[9] None of these patients received immediate adjuvant hormonal therapy.

Postoperative surveillance included PSA measurement and physical examination at 6 weeks, every 6 months for 5 years and annually thereafter. BCR was defined as PSA 0.1 ng/ml or greater with 1 confirmatory increase in detectable PSA. BCR was the outcome measured in this study.

Pathological Examination

RP specimens were serially sliced in 3 to 5 mm sections, whole mounted and entirely submitted according to previously published methods.[10] All LN specimens were separately sent for permanent section pathological analysis. Frozen section analysis was not done. After fixation in 10% neutral buffered formalin, LNs were dissected and manually counted by the pathologists. The number of positive LNs was recorded and the size of metastatic nodes was measured in cm. LNs were examined for ENE, defined as prostate cancer cells outside the LN capsule infiltrating into perinodal tissue. Each identified node was cut when appropriate, embedded in paraffin, sectioned at 5 μm, stained with hematoxylin and eosin, and examined under the microscope. No immunohistochemical stains for keratin or PSA were used.

Pathological LN slides were re-reviewed for a subset of 96 patients to measure the size of metastatic LNs in mm and the size of the metastatic focus in the LNs. Two pathologists (SWF and LJT) blinded to the study outcome (BCR) evaluated RP and LN specimens.

Statistics

We determined whether the additional pathological factors could improve the discrimination of a model predicting BCR compared to that of a base model including well-known prognostic factors. We used Cox proportional hazards regression to test the marginal significance of the additional pathology findings, including ENE (dichotomized as yes vs no) and metastatic nodal size (continuous), in a model containing other covariates known to predict BCR, including EPE, SVI, pathological Gleason score (6–7 vs 8–10), pretreatment PSA and number of positive LNs (1 or 2 vs 3 or greater). We further investigated the role of LND, calculated as the number of positive nodes divided by the total number of LNs removed and shown as a percent (continuous) since recent studies indicated its prognostic importance.[1,11–14]

Subset analysis was performed in the 96 patients whose pathology slides were re-reviewed, also including the size of the largest LNM focus (continuous variable). The characteristics of this subset were compared to those of the overall cohort. Complete data were available on 91 of the 96 patients in this subset.

The Harrell concordance index was calculated using tenfold cross validation. Recurrence-free survival was estimated by the Kaplan-Meier method with $p < 0.05$ considered significant. All analyses were done with Stata® 12.0.

RESULTS

Table 1 lists patient characteristics. Median age at surgery was 61 years and median preoperative PSA was 7.9 ng/ml. Of the patients 72% had palpable tumors.

Histopathological examination of RP specimens revealed EPE in 92% of cases and positive surgical margins in 36%. The median number of LNs removed was 14 (IQR 9, 20, range 2 to 48). The median number of positive LNs was 1 (IQR 1, 2, range 1 to 18) and 49 patients (19%) had more than 3 positive LNs. Median maximum diameter of the largest metastatic LN was 9 mm and 46% showed ENE (table 1). At a median followup of 4.6 years (IQR 3.2, 6.0) 155 of 261 patients experienced BCR, corresponding to a mean 5-year BCR-free survival rate of 39% (95% CI 33–46, see figure).

On Cox regression RP specimen Gleason score (8–10 vs 6–7), number of positive LNs (3 or greater, vs 1 or 2), SVI and PSA were statistically significant independent predictors of BCR that increased risk (table 2). No additional predictors from the extended pathological review significantly improved model