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ANATOMICAL PATHOLOGY

Prognostic significance of lymphatic, vascular and perineural invasion for bladder cancer patients treated by radical cystectomy

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Summary

In radical cystectomy specimens with bladder cancer, lymphatic and vascular invasion are often reported as 'angiolymphatic' or 'lymphovascular' invasion, terms that combine the findings of tumour within simple endothelial-lined lymphatic spaces and tumour within muscle-lined blood vessels. It is unclear if these patterns of invasion have different prognostic significance. In addition, there are conflicting data regarding the significance of lymphatic, vascular and perineural invasion in patients with bladder cancer. Herein, we studied 1504 patients treated by radical cystectomy for bladder cancer at our institution and followed for a mean of 10.6 years. Cases were re-reviewed by a urological pathologist for lymphatic invasion defined as tumour within a non-muscle-lined endothelial-lined lymphatic space, vascular invasion defined as tumour in a muscle-lined blood vessel, and perineural invasion defined as tumour within the perineural sheath. Associations of clinical and pathological features with bladder cancer death were evaluated using Cox proportional hazards regression models and summarised with hazard ratios and 95% confidence intervals. Survival was estimated by the Kaplan–Meier method. Multivariate analysis showed that lymphatic and vascular invasion but not perineural invasion were significantly associated with cancer specific survival ($p < 0.0001$ and $p = 0.02$, respectively). There was a significant association of lymphatic and vascular invasion but not perineural invasion with involved regional lymph nodes ($p < 0.0001$ and $p = 0.004$, respectively). In patients with metastasis to regional lymph nodes, lymphatic invasion remained significantly associated with outcome ($p = 0.02$). The frequency of lymphatic and vascular invasion varied amongst histological subtypes of bladder cancer. Vascular and lymphatic invasion should be clearly defined and reported for radical cystectomy specimens containing bladder cancer.

Key words: Urothelial cancer; radical cystectomy; lymphatic invasion; vascular invasion; perineural invasion; survival; recurrence.

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INTRODUCTION

There is conflicting evidence for the prognostic significance of lymphatic invasion, vascular invasion, and perineural invasion in patients with bladder cancer treated by cystectomy.[1–3] In addition, many studies have combined invasion within lymphatics (non-muscle-lined endothelial-lined space) and muscle-lined blood vessels as 'angiolymphatic' or 'lymphovascular' invasion in their analyses.[4–10] However, it is unknown if the prognostic significance of lymphatic invasion differs from vascular invasion. In addition, there is a paucity of data regarding the importance of perineural invasion in radical cystectomy specimens. Finally, nearly all previously published studies lack central pathological review, and none have considered the variant histologies of bladder cancer in their analyses.

The objective of this study was to examine a large cohort of surgically treated bladder cancer patients to determine the significance of lymphatic, vascular, and perineural invasion in predicting bladder cancer specific survival. The study included review of all cases by a urological pathologist and variant histologies.

MATERIALS AND METHODS

This study was approved by the Mayo Clinic Institutional Review Board. We identified 1504 patients with bladder cancer consecutively treated by radical cystectomy at our institution between 1980 and 2010. Clinical variables retrieved from the clinical record included age, gender, Eastern Cooperative Oncology Group (ECOG) performance status, Charlson Comorbidity Index, smoking status, body mass index, history of intravesical therapy, preoperative hydronephrosis, and preoperative (neoadjuvant) and postoperative chemotherapy. A urological pathologist (JCC) was blinded to the patient outcomes and re-reviewed all of the haematoxylin and eosin (H&E) stained slides for histological subtype, tumour grade, stage, lymphatic invasion, vascular invasion, and perineural invasion. Vascular invasion was defined as tumour cells within or invading into a muscle-lined blood vessel (Fig. 1A), lymphatic invasion was defined by the presence of nests of tumour cells within the non-muscle lined endothelial-lined lymphatic space (Fig. 1B), and perineural invasion was defined by the tumour invasion into the perineural sheath or endoneurium (Fig. 1C). It is understood that capillaries are histologically identical to lymphatics but for the purposes of this study, we restricted the term to lymphatic invasion rather than capillary-lymphatic to avoid confusion with angiolymphatic and lymphovascular invasion. The patterns of invasion were assessed at the leading edge of the tumour. Immunohistochemical markers for endothelial cells were not performed as they are not part of

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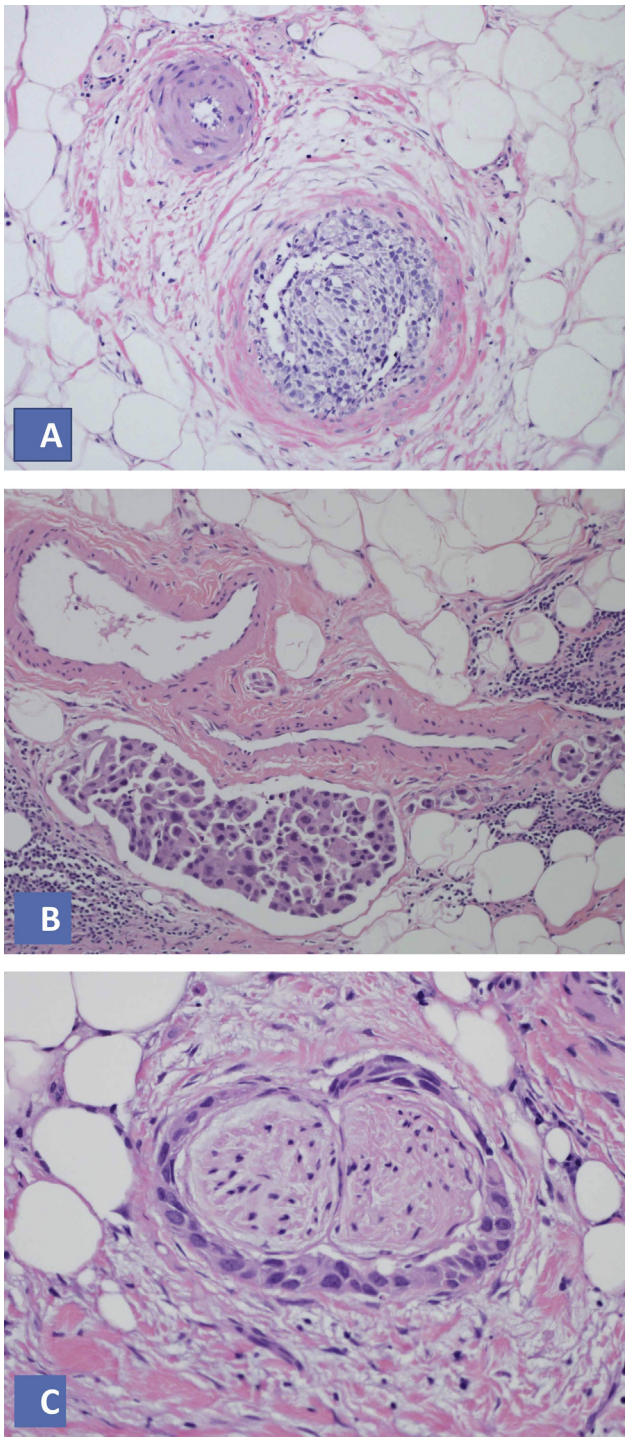

Fig. 1 (A) Vascular invasion showing tumour cells within venule with attenuated smooth muscle lining (H&E); (B) lymphatic invasion showing tumour cells within the single endothelium lined lymphatic space (H&E); (C) Perineural invasion showing tumour cells surrounding a nerve fibre (H&E).

routine clinical practice in assessment of lymphatic invasion, and not included in other large studies examining the significance of lymphatic invasion in bladder cancer.

Post-operative assessment at our institution is not standardised, but typically was performed every 4 months in the first year, biannually for second and third years, and annually thereafter as described previously.[11] Group statistics were presented as mean (standard deviation) for continuous variables and number (%) for categorical variables. Group differences were tested using t-test for continuous variables and chi-square/Fisher's exact test were used for categorical variables. Cancer specific survival was estimated using the Kaplan–Meier method. Bladder cancer survival was estimated using univariate and multivariate Cox proportional hazards regression analysis and summarised with the hazard ratio (HR) along with 95% confidence interval (CI). Statistical analysis was performed using the SAS software (SAS, USA). All tests were two-sided and the variables with a p value <0.05 were considered as statistically significant. Analyses were performed on all patients (typical urothelial carcinoma and variants), and patients with typical urothelial carcinoma only, and further stratified into lymph node negative and positive patients.

RESULTS

The clinical and pathological characteristics of the entire cohort are presented in Table 1. A total of 965 (64%) patients did not have lymphatic, vascular or perineural invasion and served as the reference group, while 306 (20%) patients had lymphatic invasion only, 59 (4%) patients had vascular invasion only, 54 (4%) patients had perineural invasion only, 36 (2%) patients had lymphatic and vascular invasion, 49 (3%) patients had lymphatic and perineural invasion, 21 (2%) patients had vascular and perineural invasion, and 14 (1%) patients had all three patterns of invasion. Higher tumour stage was associated with lymphatic, vascular, and perineural invasion ($p < 0.0001$), and lymphatic invasion and vascular invasion were significantly associated with lymph node metastases (50% of patients had positive lymph nodes with lymphatic invasion, and 32% of patients had positive lymph nodes with vascular invasion compared to 17% for the reference group, $p < 0.0001$ and $p = 0.004$, respectively). There was no difference in lymph node positivity between patients with perineural invasion and the reference group. Supplementary Table 1 (Appendix A) presents the frequency of metastasis to various organs including lymph node, lung, liver, and bone, in all four groups, and there was no predilection for a specific distant metastatic site based on type of invasion. The frequency of the patterns of invasion is varied by histological subtype (Table 2). Vascular invasion occurred more frequently in squamous cell carcinoma while lymphatic invasion was more common in micropapillary carcinoma. Figure 2A and 2B represent Kaplan–Meier survival analysis in all patients, and patients with typical urothelial carcinoma only, respectively. Survival analyses of node negative and node positive groups are shown in Fig. 3A,B, respectively.

Univariate and multivariate analyses for all cases and cases restricted to typical urothelial carcinoma are presented in Tables 3 and 4. In univariate analysis for both groups, cancer specific survival was significantly associated with tumour stage, margin positivity, adjuvant chemotherapy, lymphatic invasion, and vascular invasion. In multivariate analysis, lymphatic and vascular invasion remained significantly associated with cancer specific survival in all cases ($p < 0.0001$ and $p = 0.02$, respectively) and in cases of typical urothelial carcinoma ($p < 0.0001$ and $p = 0.0005$, respectively). Perineural invasion was not associated with bladder cancer specific survival in either univariate or multivariate analysis.

We stratified patients into node negative (pN0) and node positive (pN1–3) groups based on lymph node metastasis. Tables 5 and 6 present univariate and multivariate analyses in pN0 and pN1–3 groups. In pN1–3 patients, lymphatic invasion remained significantly associated with cancer specific survival in multivariate analysis ($p = 0.02$).

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