

**Original contribution**

Clinical significance of prominent retraction clefts in invasive urothelial carcinoma ^{☆,☆☆}



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Summary Micropapillary morphology in invasive urothelial carcinoma is an established predictor of aggressive disease. It is unknown, however, if prominent retraction is associated with more aggressive disease in the absence of classic micropapillary morphology. We reviewed a retrospective series of 309 radical cystectomy specimens with clinical follow-up data and documented the presence or absence of invasive urothelial carcinoma with *prominent retraction clefts*, defined as invasive carcinoma with retraction involving the majority of invasive tumor nests in at least one 100× field but without classic micropapillary morphology. Invasive carcinomas with plasmacytoid, sarcomatoid, nested, and small cell morphology were excluded, as were cases without lymph node sampling. In invasive conventional urothelial carcinoma, the presence of prominent retraction clefts was associated lymph node metastasis (odds ratio 4.7, $P = .0015$, Fisher exact test) but not pathologic tumor stage or several other oncologic parameters (all P s > .10). Similarly, invasive urothelial carcinoma with micropapillary morphology had lymph node metastasis more frequently than conventional urothelial carcinoma without prominent retraction clefts ($P < .001$, Fisher exact test), but there was no difference in pathologic tumor stage or oncologic parameters (all P s > .10). There was no statistically significant difference in rates of lymph node metastasis between invasive urothelial carcinoma with micropapillary morphology and conventional urothelial carcinoma with prominent retraction clefts ($P = .54$, Fisher exact test). The findings suggest that prominent retraction in invasive urothelial carcinoma may be associated with more aggressive disease, even in the absence of classic micropapillary morphology.

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1. Introduction

Invasive micropapillary urothelial carcinoma is a histomorphologic variant of bladder cancer that appears as small invasive tumor nests with prominent retraction [1]. This variant is clinically important, as it is associated with high pathologic tumor and nodal stage [2,3], resistance to intravesical immunotherapy [4], and high mortality [2,5]. However, it has been shown that

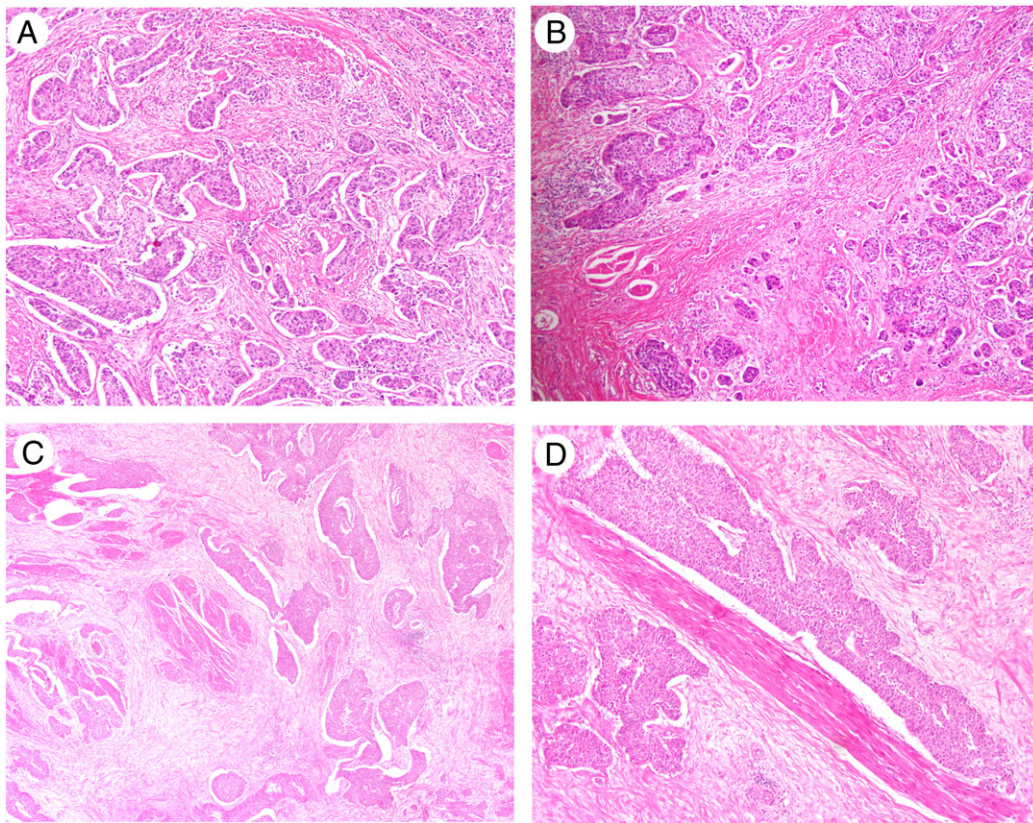


Fig. 1 Prominent retraction clefts. Tumors in many cases were admixture of small and large invasive nests with retraction clefts (A and B, original magnification $\times 100$ and $\times 40$). Viewed in isolation, the small nests have a similar appearance to micropapillary carcinoma. Other cases were composed of only large nests with retraction (C and D, $\times 40$ and $\times 100$). Prominent retraction clefts are seen in all cases as retraction around the majority of invasive nests, which is easily seen from low-power magnification.

diagnostic reproducibility of micropapillary morphology is only moderate, with diagnostic disagreement particularly in invasive carcinomas with an admixture of small and large nests with prominent retraction [6]. To our knowledge, no study has directly compared classic micropapillary urothelial carcinoma to invasive urothelial carcinoma with prominent retraction (but lacking features of classic micropapillary urothelial carcinoma) in terms of pathologic staging parameters and clinical outcomes. We thus set out to perform such a study.

2. Materials and methods

2.1. Case selection and slide review

This study was performed with Institutional Review Board approval at Penn State University College of Medicine. A consecutive series of cystectomy and cystoprostatectomy specimens was collected from the pathology archives of Milton S. Hershey Medical Center Penn State Health, including all radical cystectomies and cystoprostatectomies performed for bladder cancer from May 2001 to February 2014 ($N = 309$, excluding cases for which slides were not available). Clinical history and follow-up data were collected by medical record review.

Pathology slides were assembled, and all sections of bladder and prostate were methodically re-reviewed by study pathologists (J. I. W. and G. C.). All diagnostic slides were reviewed by a subspecialized urologic pathologist with fellowship training (J. I. W.).

2.2. Morphologic evaluation and study definitions

Carcinoma with prominent retraction clefts was defined as invasive conventional urothelial carcinoma with retraction involving the majority of invasive tumor nests in at least one $100\times$ field. We required this to be apparent from low power ($40\times$). Examples are presented in Fig. 1. Cases with micropapillary morphology were not classified as having prominent retraction clefts. Micropapillary morphology was defined strictly per World Health Organization criteria—namely, invasive urothelial carcinoma composed of small nests and aggregates without fibrovascular cores, with surrounding lacunae (often several in the same lacunar space) and peripherally oriented nuclei with atypia [1]. Cases with admixed small and large cell nests with prominent retraction were not considered micropapillary in this study. A case was designated as micropapillary urothelial carcinoma if any fraction of the invasive carcinoma had micropapillary morphology. Examples of invasive carcinoma with micropapillary morphology are presented in Fig. 2.

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