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A new system for substaging pT1 papillary bladder cancer: a prognostic evaluation

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Summary Superficially invasive (pT1) papillary urothelial cell carcinomas (UCCs) may run a variable course. Several attempts have been made for the substaging of UCC to identify the clinically aggressive tumors. We present a new substaging system, based on the extent of invasion. From a series of 53 primary pT1 UCC, 24 cases showed invasion of the subepithelial stroma by an invasive front extending more than a maximum length of 0.5 mm (pT1mic), and 29 showed extensively (>0.5 mm) infiltrating UCC (pT1ext). We tested diagnostic reproducibility between 2 pathologists and found 81% agreement. Furthermore, all cases were analyzed for mutations in the fibroblast growth factor receptor 3 (*FGFR3*) gene, which represents the favorable pathway of urothelial cell carcinogenesis. Mutant *FGFR3* was commonly observed in pT1mic UCC (15/24, 63%), but rarely (2/29, 7%) in pT1ext UCC (χ^2 test, $P < .001$). The presence of pT1ext at initial diagnosis proved to be the strongest predictor for progression, also when adjusted for *FGFR3* mutation status in a Cox regression model. If confirmed on a larger series of pT1 UCC, this relatively simple and new substaging system for pT1 UCC may prove to be of prognostic value and supportive to clinical decision-making.

1. Introduction

The clinical course of superficial (pTa and pT1) papillary urothelial cell carcinoma (UCC) is characterized by a high tendency to recur (up to 70%) and a propensity to progress in grade (10%-30%) or stage (10%-15%) [1]. The follow-up policy and treatment of patients with superficial UCC predominantly depends on conventional parameters, such as grade and stage, and the associated presence of flat lesions, such as carcinoma in situ (CIS) [2,3]. For the subset of papillary superficial UCC that invades into the subepithelial connective tissue (pT1), the clinical management is not standardized because the biological behavior of individual cases remains elusive [4,5]. Besides, molecular

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data point at the heterogeneous nature of pT1 UCC [6]. Clinicians are inclined to treat pT1 tumors, in particular, the ones with high grade in combination with CIS, more aggressively because of their higher risk of progression to muscle invasive UCC [7,8].

The depth of tumor infiltration in the submucosa has been put forward as an approach to perform substaging in pT1 UCC. This could be done by direct measurement of the depth of invasion with a micrometer or by the assessment of invasion relative to the muscularis mucosa or vascular plexus [9,10]. These methods have not yet gained a wide acceptance [11]. A more simple approach for subdividing papillary pT1 UCC may be to measure the maximum length of the invasive front, parallel to the overlying epithelium, to distinguish microinvasion (pT1mic) from "extensive" (pT1ext) infiltration. This method may be less dependent on orientation of the tissue specimen and represents a practical definition that is generally applicable. To validate this approach, the pT1mic and pT1ext UCCs were compared with regard to (1) conventional and molecular grading, which includes the fibroblast growth factor receptor 3 (*FGFR3*) mutation status [12], and (2) recurrence rate and progression during follow-up. In addition, the interobserver agreement of 2 pathologists for this substaging system was tested.

2. Materials and methods

2.1. Patients and follow-up

We extracted 63 formerly diagnosed pT1 UCC tumors from a previously described cohort of 286 patients with papillary UCC [12]. After central pathological review (T. H. van der Kwast) of the pT1 tumors, 53 tumors remained for evaluation. For comparison, the files of 131 patients with pTa UCC were retrieved to obtain data on their follow-up. The patients were seen at the Department of Urology at the Erasmus Medical Center, Rotterdam (n = 33), and at the Sint Franciscus Gasthuis, Rotterdam (n = 20). The mean age of patients at diagnosis was 68 ± 10 years (range, 47-90 years). All patients were diagnosed with UCC for the first time. After first diagnosis, 42 patients (79%) were treated with immunotherapy or chemotherapy by intravesicle instillation during median time of follow-up of 55 months (range, 9-228 months). Ten patients (19%) died of disease, 8 patients (15%) underwent cystectomy, and 28 progressed in disease. Of these 28 diseases, tumor recurred as muscle invasive (≥pT2) in 16 (30%) patients, 9 progressed in grade (G3) with concomitant CIS, and 3 were considered as clinically progressed because of repeated recurring pT1G3 + CIS, which was treated by cystectomy.

A recurrence was counted if it occurred after at least 3 months after diagnosis. Recurrence rate was calculated as the total number of recurrences divided by the total number of months of follow-up times 12 months. Progression was defined as a histologically diagnosed recurrence with higher grade and stage or the appearance of CIS. Also included in the definition of progression was cystectomy performed on patients with recurring pT1G3 associated with concomitant CIS. Progression was the primary end point in this study because it is clinically the most relevant.

2.2. Histopathology and immunohistochemistry

Standard hematoxylin-eosin–stained slides of formerly diagnosed pT1 UCC were reviewed by a specialized genitourinary pathologist (T. H. van der Kwast) and, for comparison, graded both according to the 1973 World Health Organization (WHO) classification for urothelial neoplasm and the 1998 WHO/International Society of Urological Pathology (ISUP) system [1,13]. Tumors were staged according to WHO 2002 TNM classification guidelines [1]. All 53 specimens showed invasion into the underlying lamina propria but no infiltration into the muscularis propria.

Next, 2 different types of tumor invasion were distinguished, that is, focal or microinvasive and extensive pattern of invasion (Fig. 1). Microinvasion was defined as a single focus of invasion of the subepithelial stroma by an invasive front, parallel to the overlying (neoplastic) urothelium over a maximum distance of 0.5 mm (within 1 high-power field [HPF], objective ×40). Extensive infiltration could either be multifocal microinvasive areas or invasion by tumor areas

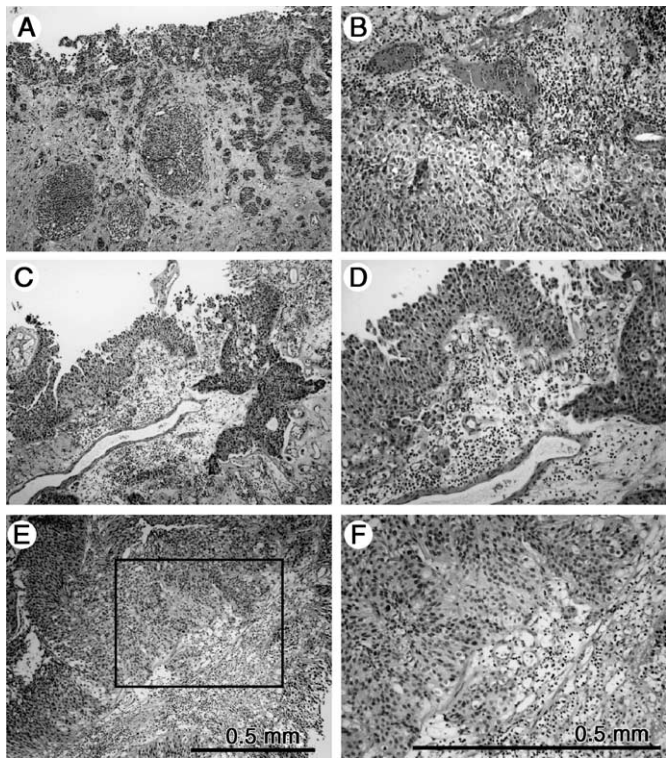

Fig. 1 Photomicrographs illustrating pT1 UCCs with extensively infiltrating (A-D) and microinvasive (E, F) patterns. In A and B, the invasive tumor fronts are not contained within 1 HPF, or multiple foci of invasion are present (C, D). Details are given at high power in B, D, and F (×200).