

## ANATOMICAL PATHOLOGY

### Long term outcome of primary urothelial papilloma: a single institution cohort

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#### Summary

The aim of this study was to investigate the long term outcome of primary urothelial papilloma (UP). We retrieved 41 primary UP, diagnosed between January 2000 and December 2009. Follow-up was obtained by searching pathology and clinical electronic databases. Mean patient age was 57 years (range 30–84 years), with a male-to-female ratio of 1.9:1. Mean follow-up was 81 months (range 3–127 months). In 37 (90.2%) patients, no recurrence and/or progression were documented and no subsequent higher grade neoplasms were diagnosed. Three male patients were diagnosed with UP at 1, 31, and 43 months after the initial resection; the repeat diagnosis of UP at 1 month likely represented an incomplete resection. Thus, only two of 41 patients (4.9%) had a recurrent UP. One of these patients had a subsequent papillary urothelial neoplasm of low malignant potential (PUNLMP), 17 months after the recurrent UP (48 months after the initial UP). Only one additional male had a subsequent PUNLMP, 76 months after the initial UP. Thus, only two of 41 patients (4.9%) had a subsequent PUNLMP, both presenting with haematuria. Primary UP does not progress to UC when diagnosed using strict criteria, when no previous or concurrent neoplasms are documented, and when complete initial resection is performed.

**Key words:** Papilloma, progression, recurrence, urinary bladder, urothelial neoplasm, urothelial papilloma.

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#### INTRODUCTION

Urothelial papilloma (UP) is a distinct and uncommon bladder neoplasm which should be distinguished from other papillary urothelial neoplasms. UP can occur either as a primary (*de novo*) neoplasm, arising without previous or concurrent urothelial neoplasms, or as a secondary neoplasm, associated with prior or concurrent urothelial tumours of higher grade. The 1998 consensus classification of the urinary bladder neoplasms by the World Health Organization (WHO) and the International Society of Urological Pathology (ISUP) established restrictive criteria for the diagnosis of UP and defined UP as a neoplasm exhibiting exophytic and discrete papillary growth with delicate fibrovascular cores covered by urothelium of normal thickness and cytology.<sup>1</sup> Although in practice many use these restrictive diagnostic criteria, some apply them more liberally, which has generated some controversy regarding the UP potential for recurrence and progression. Also in some older studies, the term 'papilloma' designated lesions which do not conform

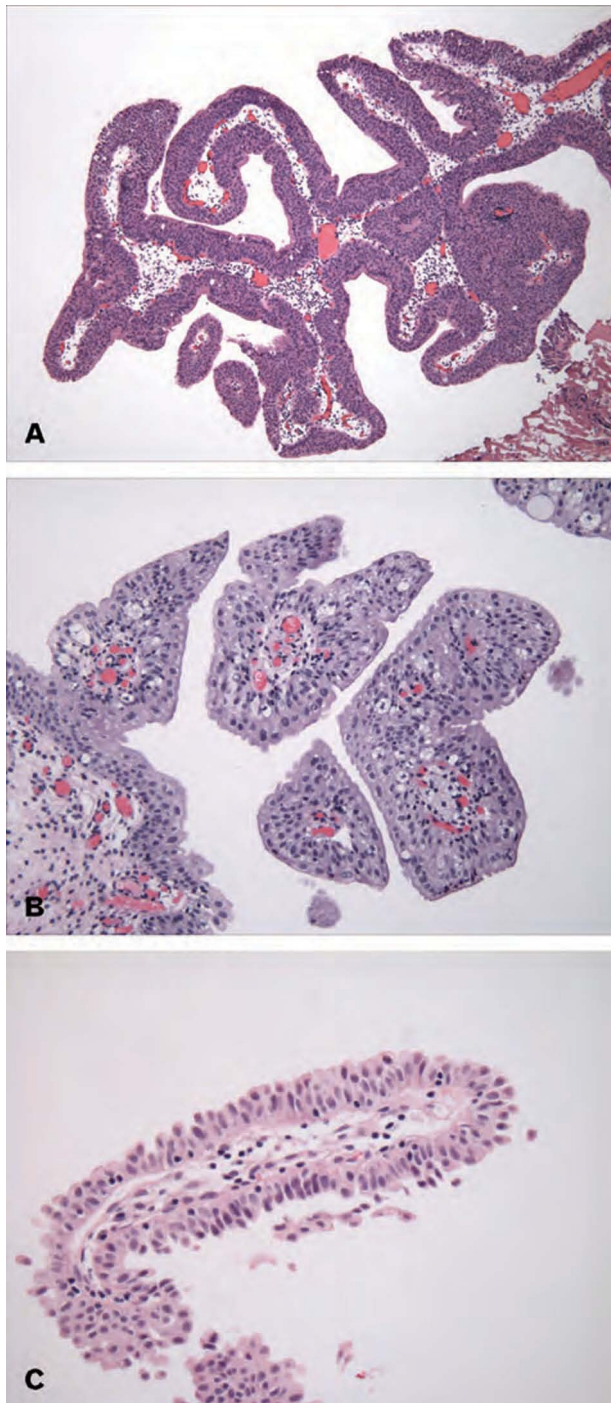
to the strict UP criteria, rendering these series difficult to compare with those more recent, using strict diagnostic criteria. Long-term clinical outcome studies of primary UP are also lacking and some studies do not specify whether primary or secondary UP were included.

UP tends to occur in younger patients and is also seen in children. Patients with primary UP are younger than those with urothelial carcinoma. UP usually presents as a single and relatively small size neoplasm, although multifocality has been documented, particularly in secondary UP, exhibiting history of prior or concurrent urothelial neoplasm. On microscopy, UP shows an exophytic growth with simple, non-branching or minimally branching and delicate fibrovascular stalks, with the fronds often detached from the urothelial surface (Fig. 1A–C). More complex papillary growth can also be seen, admixed with oedema within the papillae and sometimes papillomas even demonstrate focal endophytic (inverted) growth.<sup>1–3</sup> The diagnostic criteria do not specify the number of cell layers, indicating that urothelium should not be obviously thicker than the normal urothelium. Surface umbrella cells may vary morphologically and may be either inconspicuous or may show slightly enlarged nuclei and paler, often vacuolated cytoplasm, or may even exhibit hobnail appearance with abundant eosinophilic cytoplasm. The umbrella cell nuclei may show degenerative atypia, but otherwise, urothelial atypia is incompatible with the diagnosis of UP. UP generally lacks mitotic figures.

The reported recurrence rate for primary UP ranges from 7% to 9%,<sup>3–5</sup> and the progression rate to high grade carcinoma ranges from 2% to 9%.<sup>3–5</sup> However, the long-term biological behaviour of UP remains uncertain, because there is only one previous study with a mean follow-up longer than 5 years, which reported a recurrence rate of 8% and a progression rate of 2%.<sup>4</sup> The variations in the reported recurrence and progression rates in previous studies and the paucity of studies with long follow-up prompted us to review our institutional experience of primary UP.

#### MATERIALS AND METHODS

The study was approved by the institutional Ethics Review Board (Conjoint Regional Ethics Review Board, University of Calgary). We reviewed all consecutive cases with a diagnosis of UP during a 10-year period (from 1 January 2000 to 31 December 2009), which were retrieved from the institutional information system, in a centralised regional urology and uropathology service. All pathology slides were reviewed by three genitourinary pathologists and all cases included in the study met the diagnostic criteria for UP, according to the 2004 WHO classification. No UP exhibited mixed architecture with focal or partial inverted (endophytic) growth. The follow-up was conducted by searching pathology and clinical electronic databases.



**Fig. 1** Histological features of urothelial papilloma. (A) Urothelial papilloma exhibits delicate papillary growth with fibrovascular cores lined by normal urothelium. (B) The papillary fronds are often detached and 'float' above the urothelial surface. (C) Delicate fibrovascular core of papilloma is covered by bland urothelial lining resembling normal urothelium.

All included patients had a diagnosis of a primary (*de novo*) UP and none had a co-existent or previous diagnosis of urothelial dysplasia, carcinoma *in situ* or a higher grade or stage urothelial neoplasm. We also excluded from the study all patients demonstrating a diagnostic ambiguity and the external consult cases with uncertain follow-up. Collected clinical data included, age, gender, date of diagnosis, biopsy-documented subsequent recurrence and/or progression, and clinical symptoms during the follow-up. Presence of a biopsy-documented subsequent UP more than 3 months after the initial diagnosis of UP was considered a recurrence and any subsequent biopsy-documented higher grade or stage urothelial neoplasms, more than 3 months after the initial diagnosis, was considered a progression.

**Table 1** Clinical data in patients with primary urothelial papilloma

Age mean/median (range), years	57/56 (30–84)
Male:Female ratio	1.9:1
Follow-up mean/median (range), months	81/76 (35–127)
Patients below the age of 50 years, <i>n</i> (%)	13 (31)
Patients with no recurrence or progression, <i>n</i> (%)	37 (90.2)
Patients with recurrent UP, <i>n</i> (%)	2 (4.9)
Patients with subsequent PUNLMP, <i>n</i> (%)	2 (4.9)

PUNLMP, papillary urothelial neoplasm of low malignant potential; UP, urothelial papilloma.

## RESULTS

We identified 41 patients diagnosed with primary (*de novo*) UP, all of which were solitary lesions and were located in the urinary bladder. The clinical findings are summarised in Table 1. The average patient age was 57 years, with a male-to-female ratio of 1.9:1. Only 13 (31%) patients were below the age of 50 years, while the remaining patients were older than 50 years. The mean patient follow-up was 81 months (median 76, range 35–127 months). In 37 (90.2%) patients, no recurrent neoplasms were documented, including progression to low grade urothelial carcinoma (UC), high grade UC or carcinoma *in situ*. Subsequent urothelial neoplasms were diagnosed in four patients. Three male patients had a subsequent UP at 1, 31, and 43 months after the initial diagnosis of UP. The patient with a subsequent UP at 1 month after the initial diagnosis likely had an incomplete initial resection, rather than recurrent urothelial neoplasm. Thus, only two of 41 patients (4.9%), both male (age 59 and 77 years), had a recurrent UP. One male patient with a recurrent UP at 31 months, subsequently developed a papillary urothelial neoplasm of low malignant potential (PUNLMP), 17 months after the recurrent UP (48 months after the initial UP); his age at the time of initial diagnosis of UP was 50 years. Only one additional male patient (age 76 years) had a subsequent biopsy showing PUNLMP, 76 months after the initial UP. Both patients diagnosed with PUNLMP presented with haematuria during the follow-up.

## DISCUSSION

In the current study, which focused on the long term clinical outcome of UP, we demonstrated recurrence and progression rates of 4.9%, respectively, and confirmed that UP demonstrates an indolent behaviour when: (a) strict diagnostic criteria are used, (b) no previous or concurrent urothelial neoplasms are documented, and (c) the completeness of the initial resection can be ascertained. Two patients diagnosed with a subsequent PUNLMP, which can arguably be considered a 'progression', presented with haematuria during the clinical follow-up, which prompted a repeat cystoscopy.

UP is a rare benign neoplasm, which represents less than 3% of all papillary urothelial neoplasms.<sup>6–9</sup> Mostofi defined papilloma as a non-invasive papillary lesion covered by urothelium that is indistinguishable from the normal urothelium<sup>10</sup> and in 1973 the WHO adopted this definition.<sup>11</sup> UP has also been recognised as a separate diagnostic category in the WHO classification of urinary bladder neoplasms in 2004.<sup>12</sup> Although the definition of papilloma from the 1973 WHO classification was essentially identical to that of 2004, there are inconsistencies as to how the diagnostic criteria for UP are applied in practice, resulting in some variations in reported outcomes.

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