13.00–14.00	**ПЕРЕРЫВ НА ОБЕД**
14.00–15.40	**Сессия – Онкоурология** (председатель – Ковылина М.В.)
14.00–14.25	**Antonio Lopez-Beltran** (Испания) CIS/Dysplasia of the urothelium
14.25–14.50	**Antonio Lopez-Beltran** (Испания) Pathologic assessment of invasion in TUR specimens
14.50–15.10	**Antonio Lopez-Beltran** (Испания) Urothelial tumors with inverted growth
15.10–15.30	**Antonio Lopez-Beltran** (Испания) Variants of urothelial carcinoma
15.30–15.40	**Дискуссия – все участники**

Urothelial Tumors with Inverted Growth

A. Lopez-Beltran

Inverted Papilloma

(UROTHELIAL ADENOMA; BRUNNIAN ADENOMA) Background

- **Benign** urothelial tumor that has an inverted growth pattern with normal to minimal cytologic atypia of the neoplastic cells (WHO, 2004)

- Mostly solitary, but multifocal lesions may occur
- Less than 1% of urothelial neoplasms. M:F 4-5:1
- Age: 10 to 94 years (mean 55 years)
- Hematuria and obstruction are the most common symptoms
- Most are smaller than 3 cm but can be larger
- Neoplastic vs. reactive

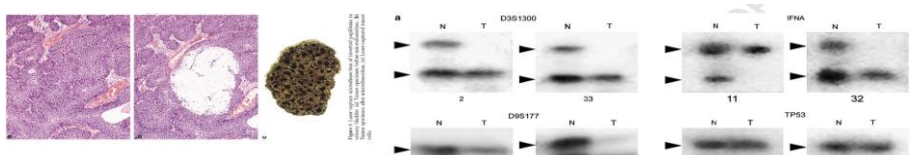


Table 1 Comparison of LOH between inverted papilloma, papillary urothelial neoplasm of low malignant potential and urothelial carcinoma

Reference	*Specimen*	*Frequency of LOH (%) chromosome region*			
		D9S177 9q32–33	*IFNA 9p22*	*TP53 17p13.1*	*D3S1300 3p14.2*
Current study	Inverted papilloma	8	8	10	8
Cheng *et al*[21]	PUNLMP	41	32	29	44
Baud *et al*[11]	Urothelial carcinoma	74			
Paterson *et al*[23]	Urothelial carcinoma	67		47	
Keen *et al*[13]	Urothelial carcinoma		60		
Uchida *et al*[24]	Urothelial carcinoma		35	39	
Primdahl *et al*[16]	Urothelial carcinoma		35	41	
Louhelainen *et al*[14]	Urothelial carcinoma				80

LOH: loss of heterozygosity; PUNLMP: papillary urothelial neoplasm of low malignant potential.

Inverted papilloma of the urinary bladder: a molecular genetic appraisal

Ming-Tse Sung[1,2,3], John N Eble[1], Mingsheng Wang[1], Puay-Hoon Tan[4], Antonio Lopez-Beltran[5] and Liang Cheng[1,6]

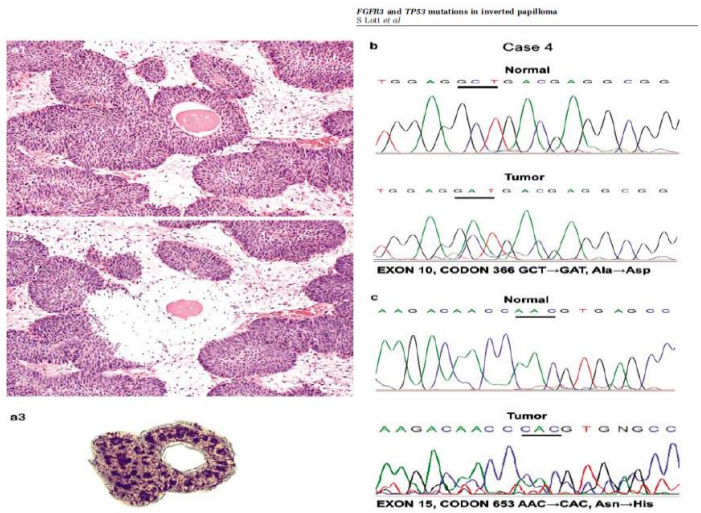
Modern Pathology (2009) 22, 627–632

www.modernpathology.org

FGFR3 and *TP53* mutation analysis in inverted urothelial papilloma: incidence and etiological considerations

Sarah Lott[1], Mingsheng Wang[1], Shaobo Zhang[1], Gregory T MacLennan[2], Antonio Lopez-Beltran[3], Rodolfo Montironi[4], Ming-Tse Sung[5], Puay-Hoon Tan[6] and Liang Cheng[1,7]

Urothelial papillomas and low-grade urothelial carcinomas have shown a high incidence of fibroblast growth factor receptor 3 (*FGFR3*) mutations and are associated with a favorable prognosis. The association of *FGFR3* mutations with inverted papillomas is less known. We analyzed 20 cases of inverted papilloma in the urinary tract. Mutations of *FGFR3* (exons 7, 10, and 15) and *TP53* genes were evaluated by DNA sequencing in these cases. Point mutations of the *FGFR3* gene were identified in 45% (9 of 20) of inverted papillomas with four cases exhibiting mutations at multiple exons. Seven cases had exon 7 mutations containing R248C, S249T, L259L, P260P, and V266M. Two cases had exon 10 and 15 mutations including A366D, H412H, E627D, D641N, and H643D; five cases had N653H. The most frequent mutation was identified at R248C. None of the inverted papillomas exhibited mutations in *TP53*. During a mean follow-up of 78 months, none had recurrence or developed urothelial carcinoma. These findings support the concept that low-grade and low-stage urothelial neoplasms arise in a background of molecular changes that are distinctly different from the molecular changes of high-grade and high-stage urothelial cancers.



¡Natural History¡

Natural History of Urothelial Inverted Papilloma

Ming-Tse Sung, MD[1,2]
Gregory T. MacLennan, MD[3]
Antonio Lopez-Beltran, MD[4]
Rodolfo Montironi, MD[5]
Liang Cheng, MD[1,6]

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University College of Medicine, Kaohs

[3] Department of Pathology, Case We
University, Cleveland, Ohio.

[4] Department of Pathology, Cordo
Cordoba, Spain.

[5] Institute of Pathological Anatomy
thology, School of Medicine, Polytec
of the Marche Region (Ancona), Uni
Ancona, Italy.

[6] Department of Urology, Indiana Uni
of Medicine, Indianapolis, Indiana.

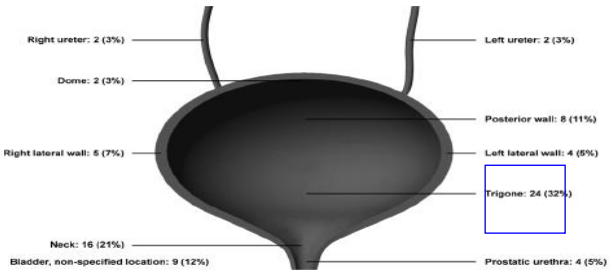


FIGURE 2. Distribution of inverted papillomas in the urinary tract.

TABLE 2
Follow-up of Inverted Urothelial Papilloma in Large Series Studies (Over 10 Cases)

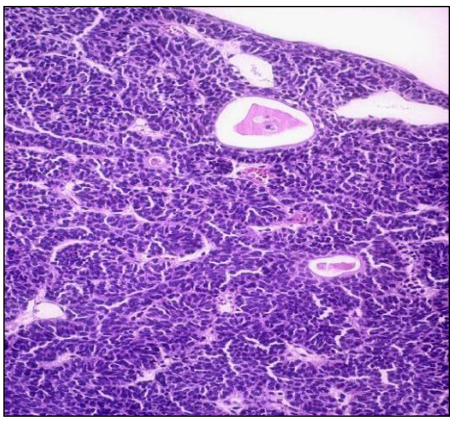
Reference	Year of publication	Case no.	Prior UC	Concomitant UC	Recurrence of IP	Recurrence or new occurrence of UC
DeMeester et al.[10]	1975	20	0 (0)*	0 (0)	1 (5)	0 (0)
Cameron and Lupton [7]	1976	35	0 (0)	0 (0)	0 (0)†	0 (0)
Aubert et al. [6]	1984	10	0 (0)	1 (10)	1 (10)	0 (0)
Mattelaer et al. [13]	1988	15	0 (0)	1 (7)	0 (0)	3 (20)‡
Witjes et al. [19]	1997	37	0 (0)	0 (0)	2 (5)	1 (3)
Cheville et al. [9]	2000	51	1 (2)	6 (12)	0 (0)	4 (8)§
Asano et al. [5]	2003	48	1 (2)	5 (10)	1 (2)	2 (4)‖
Cheng et al. [3]	2005	20	0 (0)	0 (0)	0 (0)	1 (5)
Current study		75	0 (0)	0 (0)	1 (1)	0 (0)

UC indicates urothelial carcinoma; IP, inverted papilloma.
* Values in parentheses are percentages.
† Two cases had small lesions fulgurated without further histopathological examination at 9 months and 2 years after the initial diagnosis of inverted papilloma.
‡ One case with concomitant UC.
§ Three cases with concomitant UC.
‖ One case with prior UC.

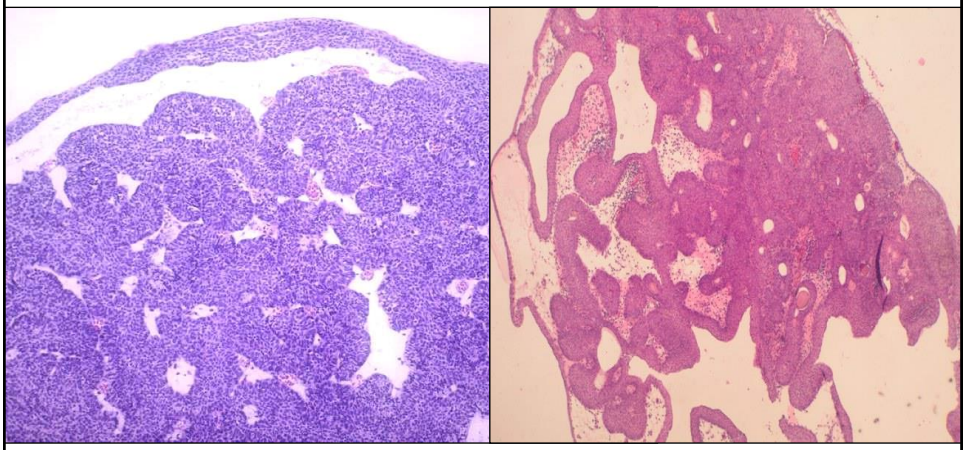
Inverted Papilloma
Histologic Characteristics

Inverted Papilloma: Histology

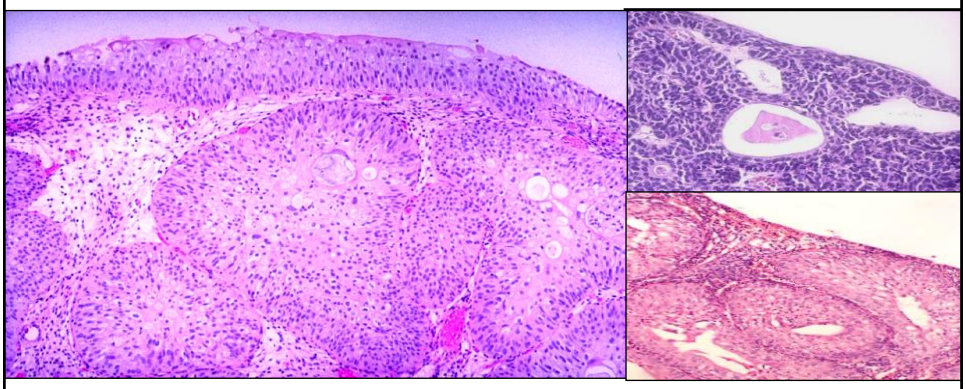
- Anastomosing islands and cords
- of urothelial cells invaginating extensively
- from the surface urothelium into the lamina propria
- but not into the muscularis propria.



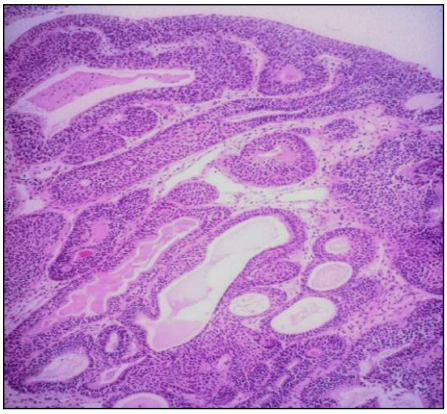
IP Gross/Histology: Polypoid Lesion
Sessile vs. Pedunculated

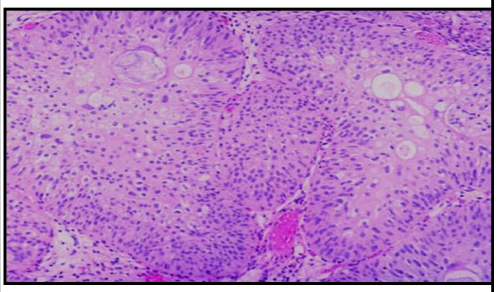


Inverted Papilloma: Histology
Surface



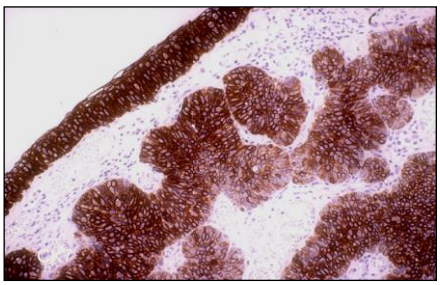
Inverted Papilloma: Histology
Cystic spaces lined by urothelium that may contain eosinophilic PAS+secretions/solid/microcysts

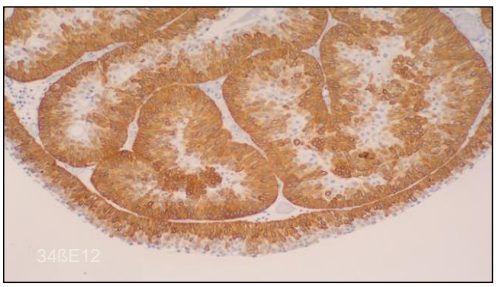




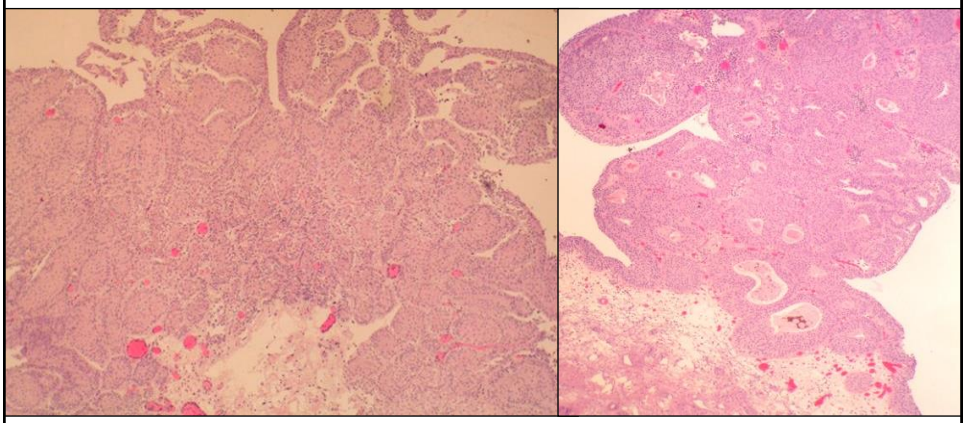
Inverted Papilloma: Histology

- In contrast to UCA, the central portion of the cords contain urothelial cells and the periphery contains palisades of basal cells

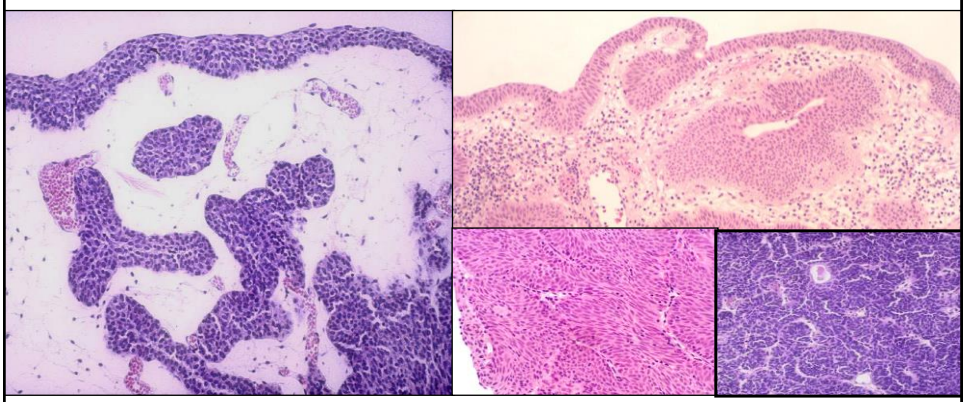




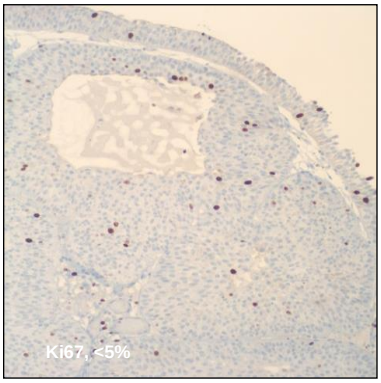
Inverted Papilloma: Histology

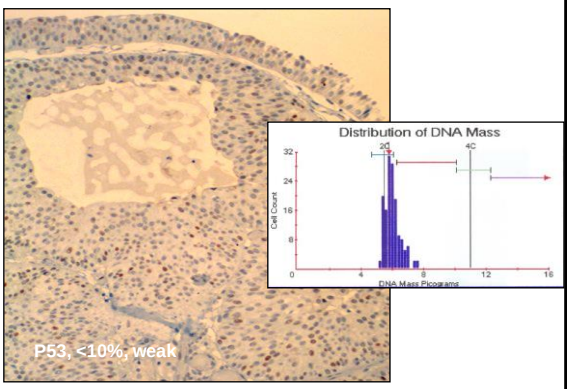


Inverted Papilloma: Histology



Inverted Papilloma: Histology
Mitotic features are rare-to-absent
Low proliferation and p53 accumulation
DNA Diploid



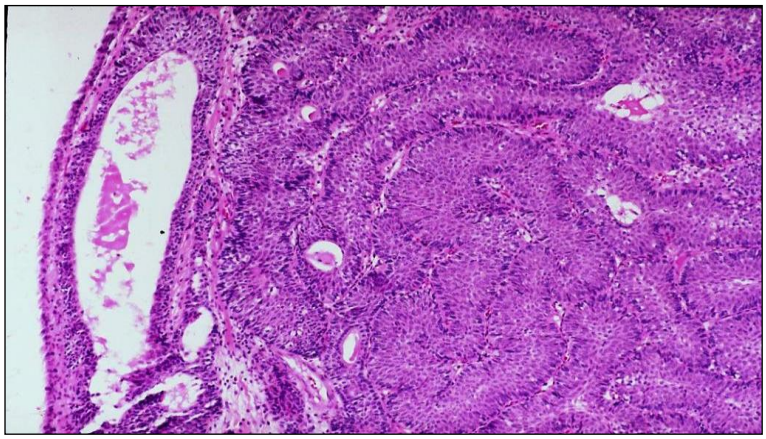


Pitfalls in Uropathology

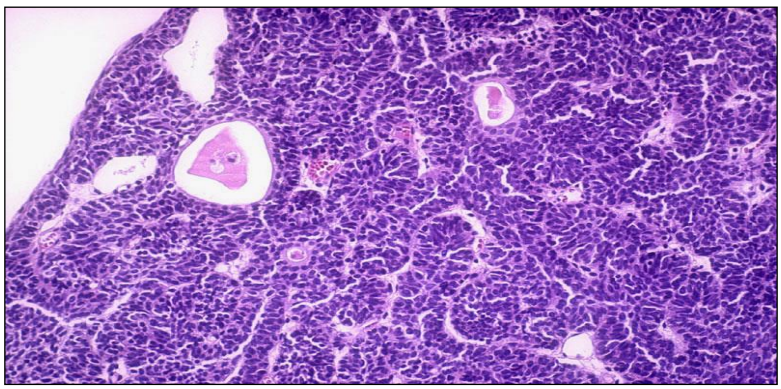
¡Histologic Variants of Inverted Papilloma¡

- Trabecular
- Glandular
- With Sq. Metaplasia
- With neuroendocrine dif. (40%).
- Medular
- Hiperplastic
- With nuclear atypia
- **Others**

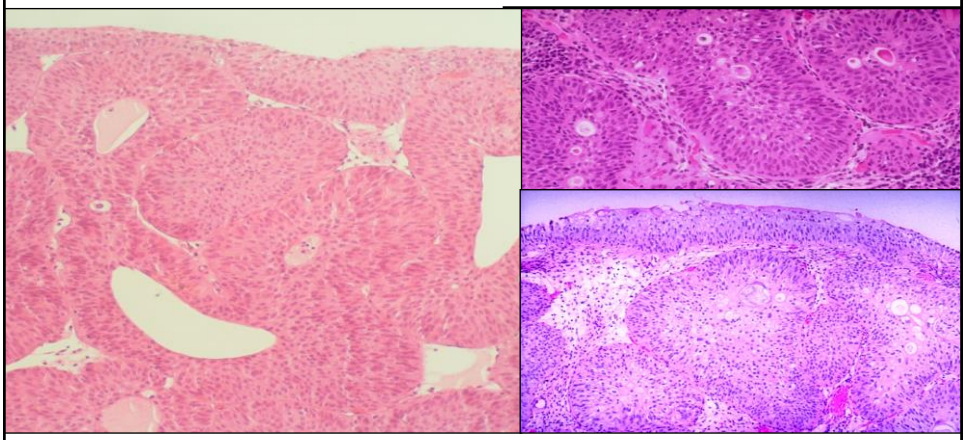
Inverted Papilloma
Trabecular type



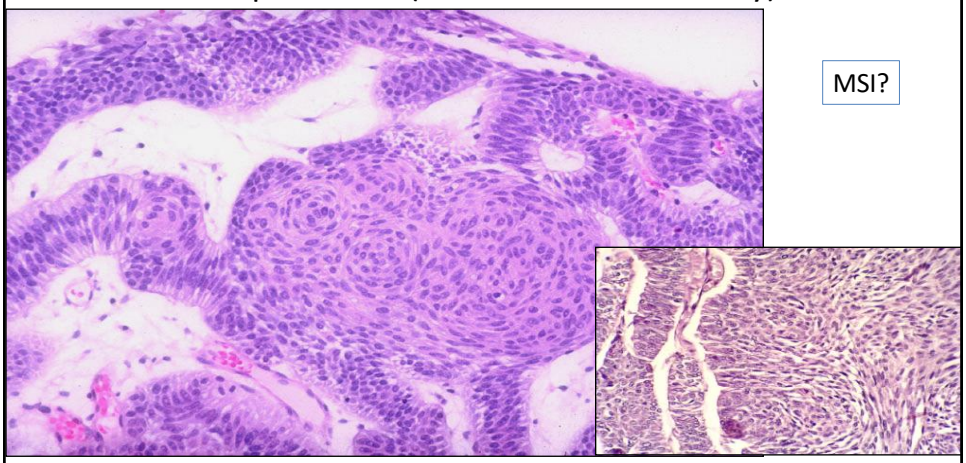
Inverted Papilloma
Basaloid



Inverted Papilloma
Hyperplastic



Inverted Papilloma
Spindle cell (also called as medullary)

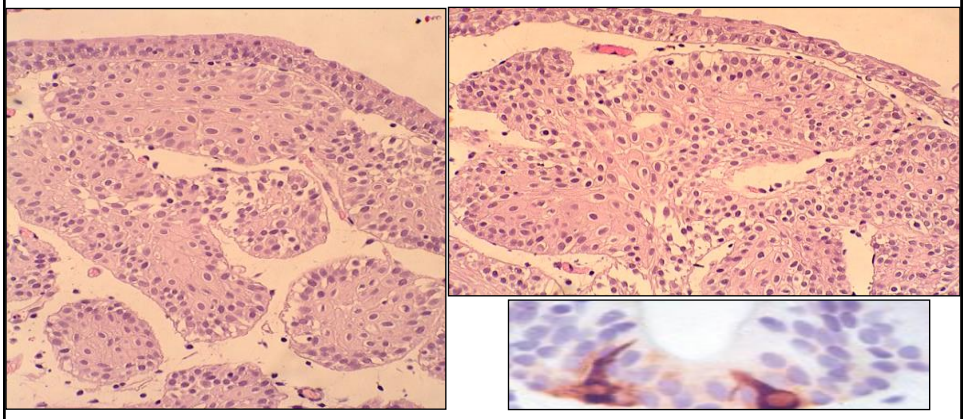


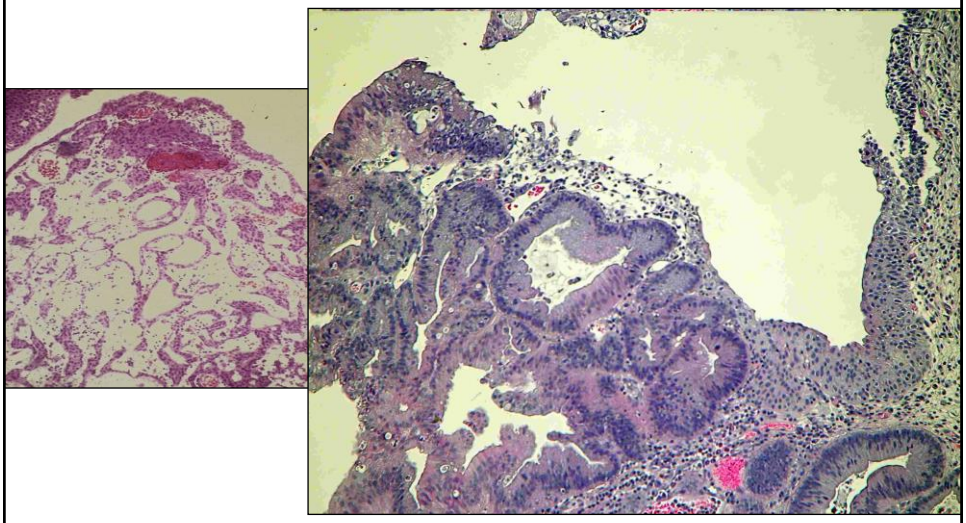
MSI?

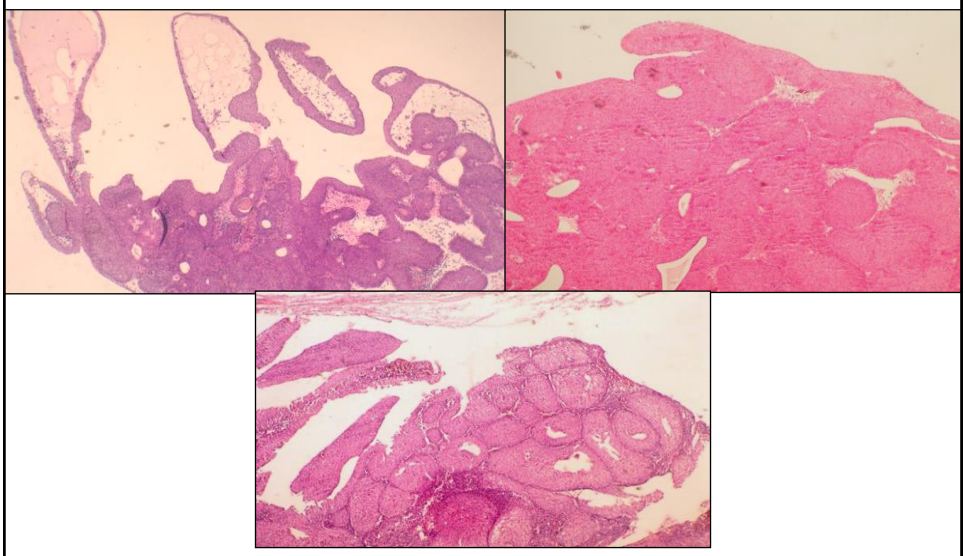
Inverted Papilloma

Non-keratinizing squamous differentiation

Neuroendocrine differentiation

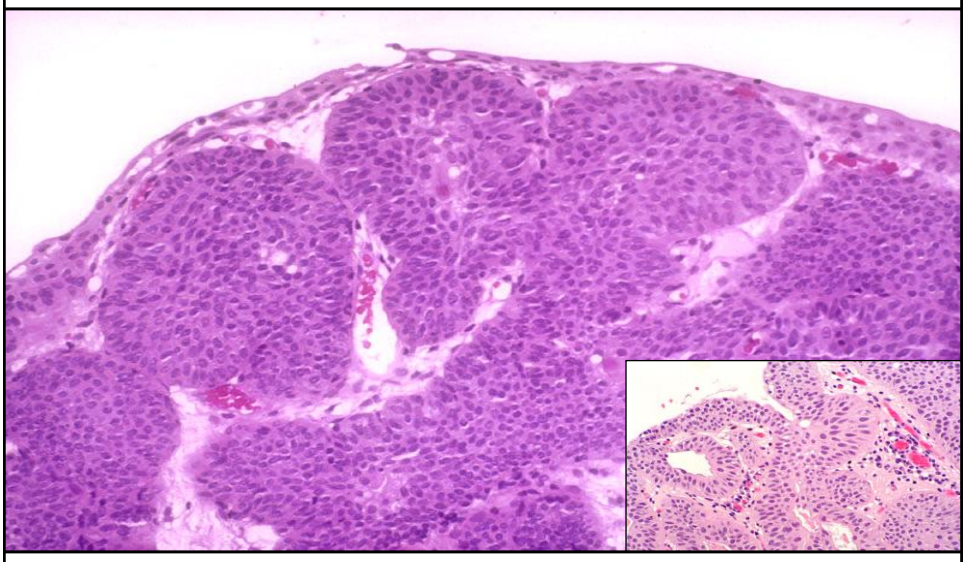


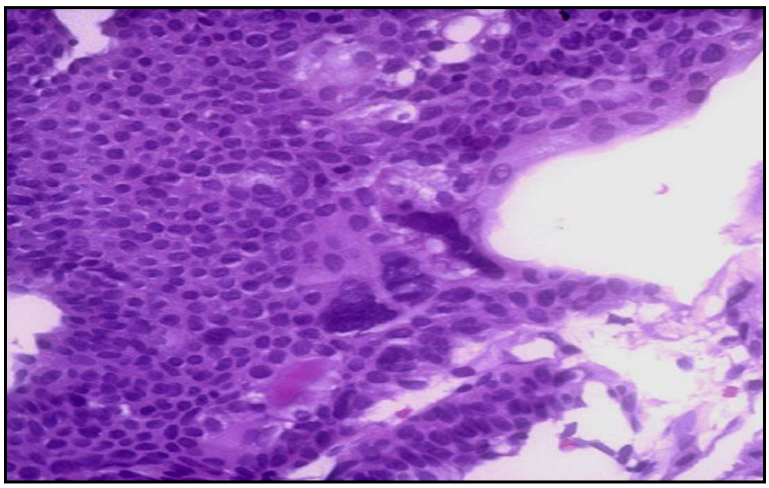




Inverted Papilloma with Atypia

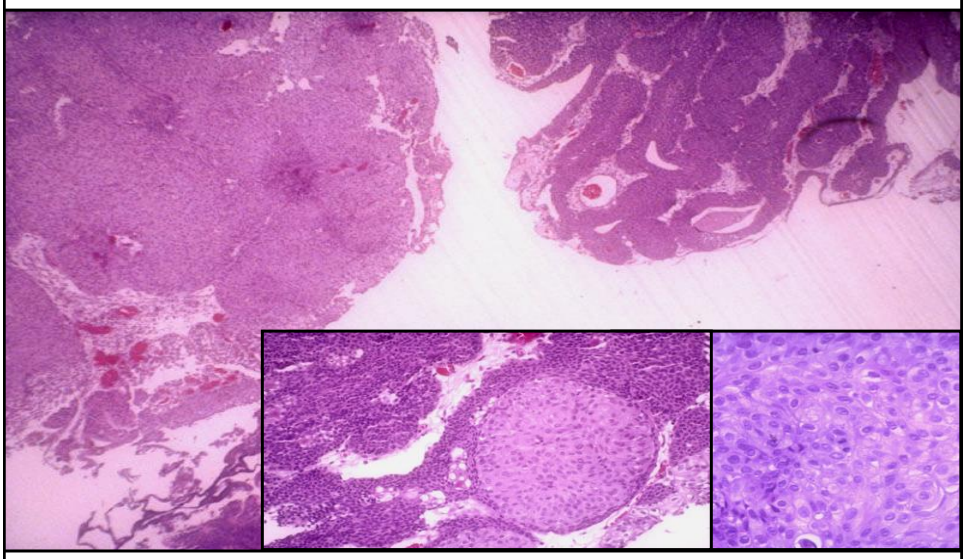
- Focal minor cytologic atypia is often seen
- In rare cases nuclear atypia may be prominent but these atypical nuclear features are most probably best considered degenerative in nature.
- These cases have rare-to-absent mitosis just like the usual IP
- To date there has been no association with urothelial carcinoma in the follow up of individuals diagnosed with inverted papilloma with atypia.





RELATIONSHIP WITH UROTHELIAL CARCINOMA

1. Association with bladder cancer (5%)
2. Urothelial carcinoma with inverted features



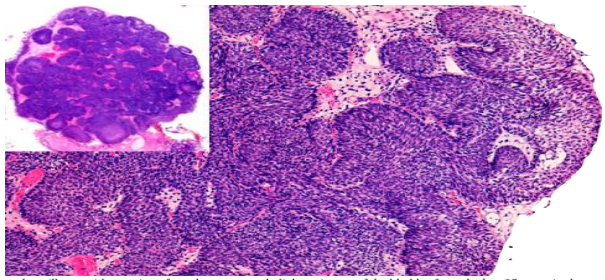
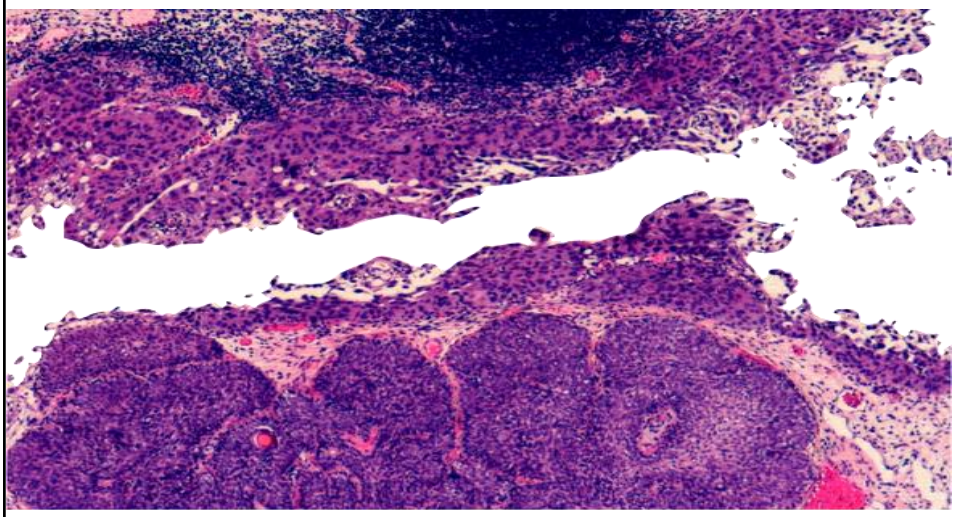
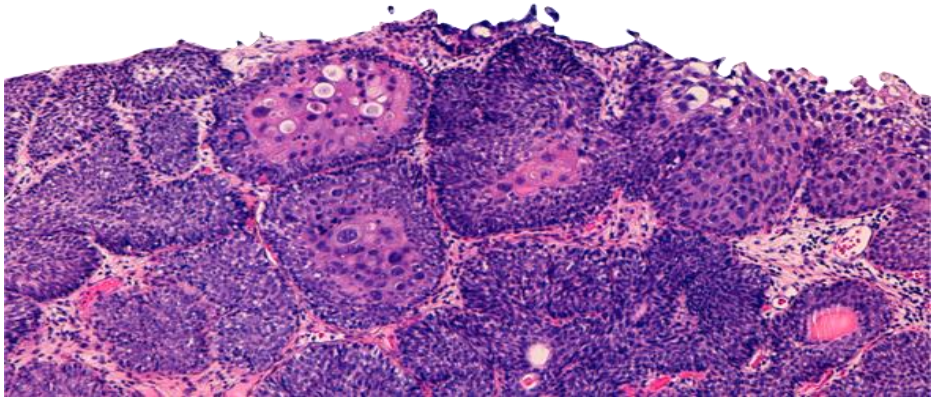


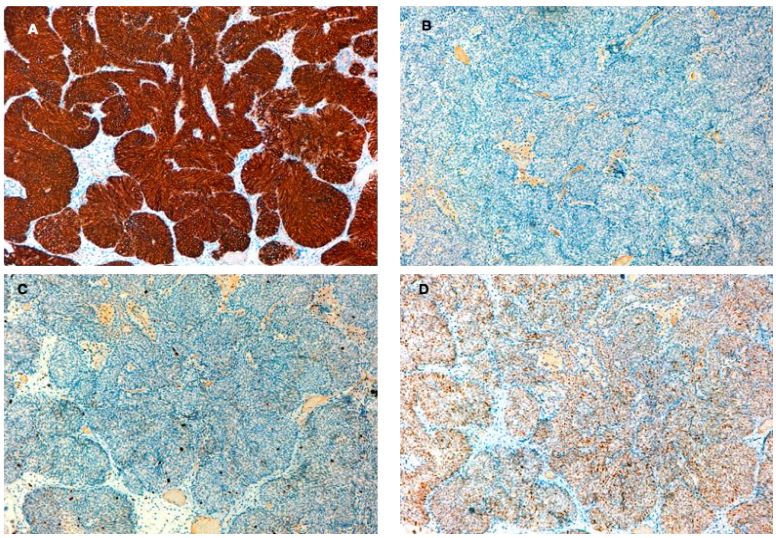
Table 1 - Cases of bladder inverted papilloma with mention of synchronous urothelial carcinoma of the bladder from the last 25 years in the english literature.

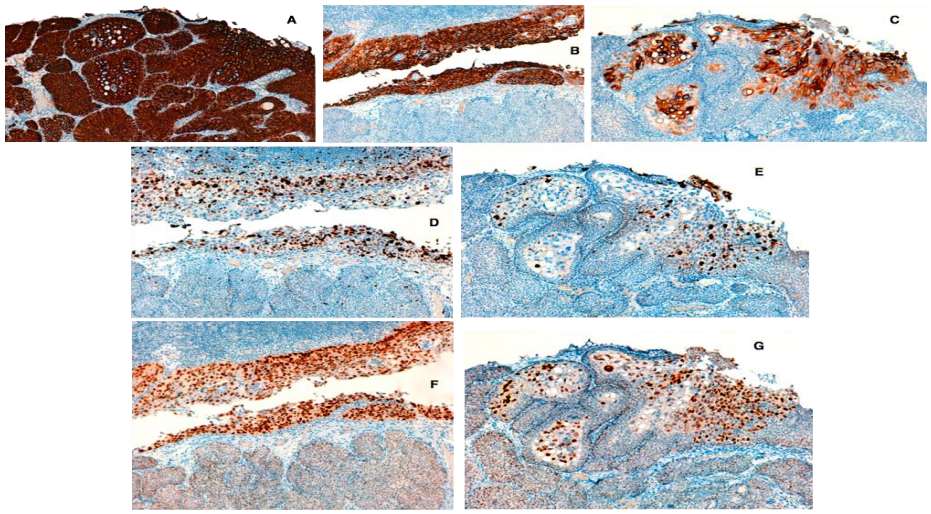
Authors	Cases of IP+UC;IP	F;M	Mean;Range Age (years)	Comments
Brown[5]	1;41	N/A	N/A	-
Asano[8]	3;48	1;2	63,3;49-71	No recurrences; Mean follow-up 67,3months (range 8-162)
Lee[9]	1;53	N/A	N/A	No recurrences
Cheville[10]	6;51	N/A	N/A	No patient died from UC or developed invasive UC
Urakami[11]	1;17	N/A	N/A	-
Behzatoğlu K[12]	1;1	0;1	71*	Patient presented with hematuria and dysuria; Follow-up 13 months
Stanfield BL[13]	1;1	1;0	54	Patient presented with hematuria and voiding difficulties
Wu TT, (cited by Cheng[6])	1;4	0;1	77*	-
Cheon[14]	1;7	N/A	N/A	Did not considered the cases described as malignant IP
Kunimi (cited by Cheng[6])	1;N/A	N/A	N/A	-

N/A - information not available; *age refers to the only patient in the study






A
B
C
D

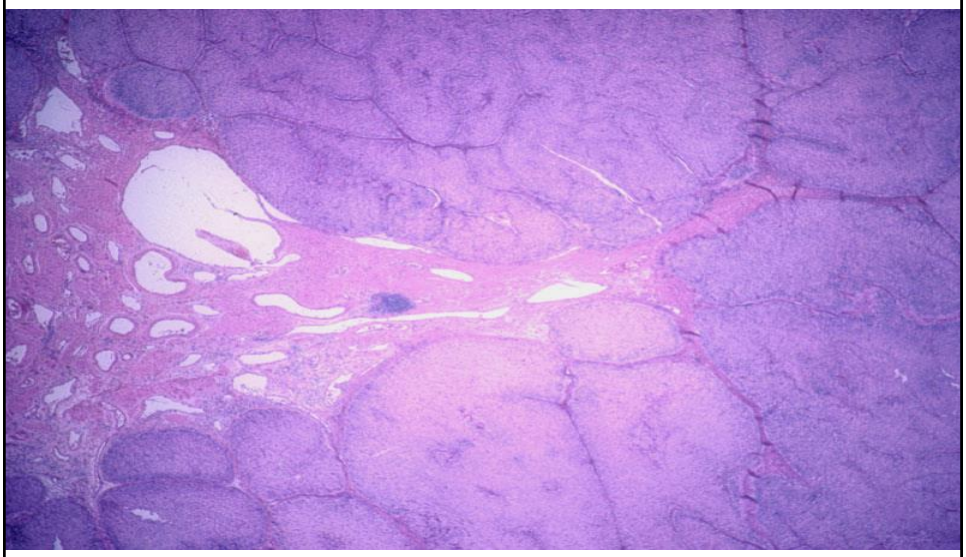


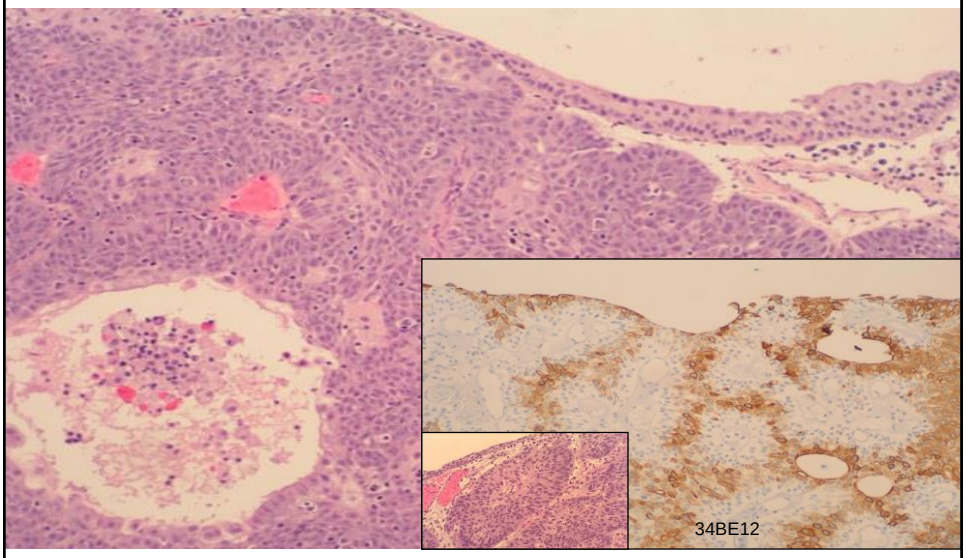
Inverted Growth Patterns of Cancer
UROTHELIAL CARCINOMA, INVERTED GROWTH

- **In 1976, Cameron and Lupton described 2 cases of urothelial carcinoma which mimicked inverted papilloma architecturally, but possessed high grade cytologic abnormalities.**
- **Amin et al 1997 discussed UCA with endophytic growth patterns and found :**
  - **Tumors having an identical architecture to inverted papilloma.**
  - **While others grow with more of a broad pushing front analogous to carcinoma.**

Inverted Growth Patterns of Cancer

- **By definition**
  - **nuclear pleomorphism, mitotic figures, and architectural abnormalities consistent with urothelial carcinoma (WHO/ISUP, 2004)**
- **In most cases, the overlying epithelium has similar abnormalities.**
- **Carcinoma with minimal cytologic and architectural abnormalities**
  - **high mitotic activity and high ki67 labeling index.**
- **An exophytic papillary or invasive component is often associated with the inverted carcinoma.**

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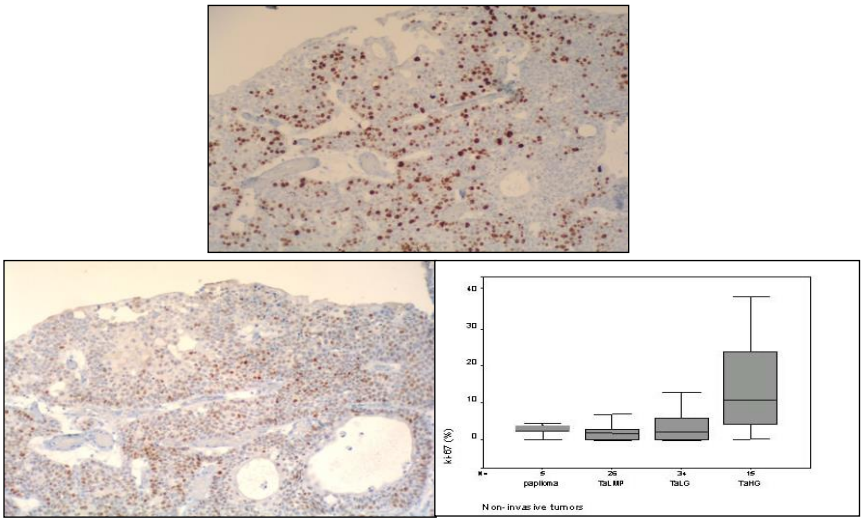
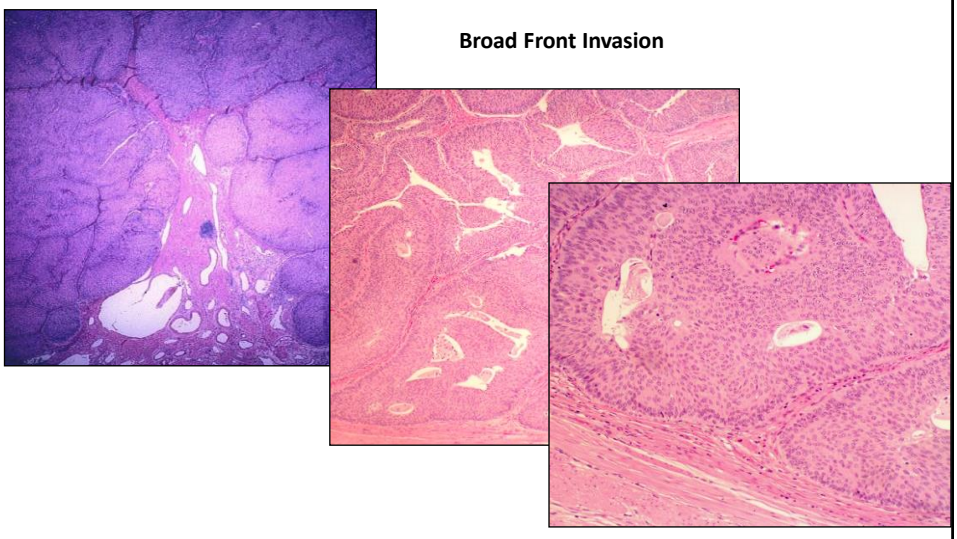
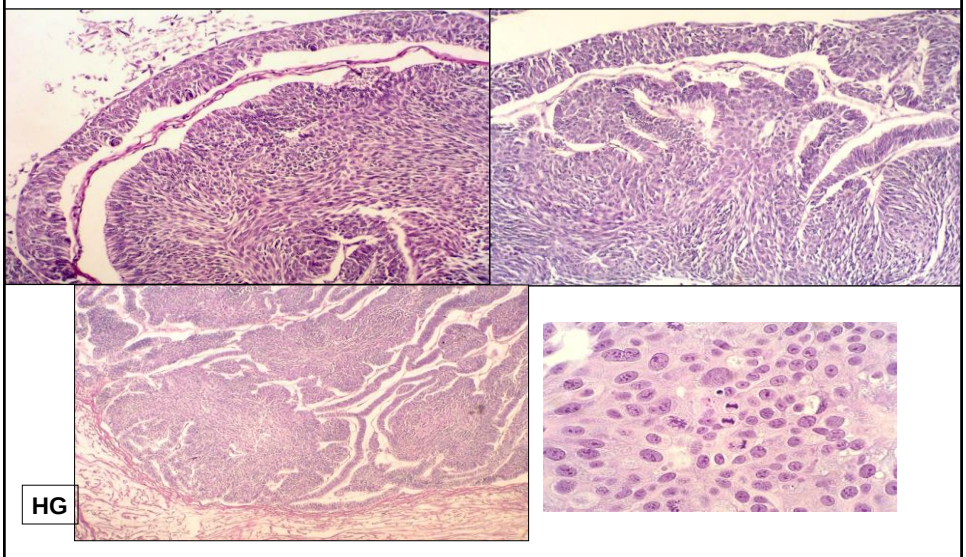
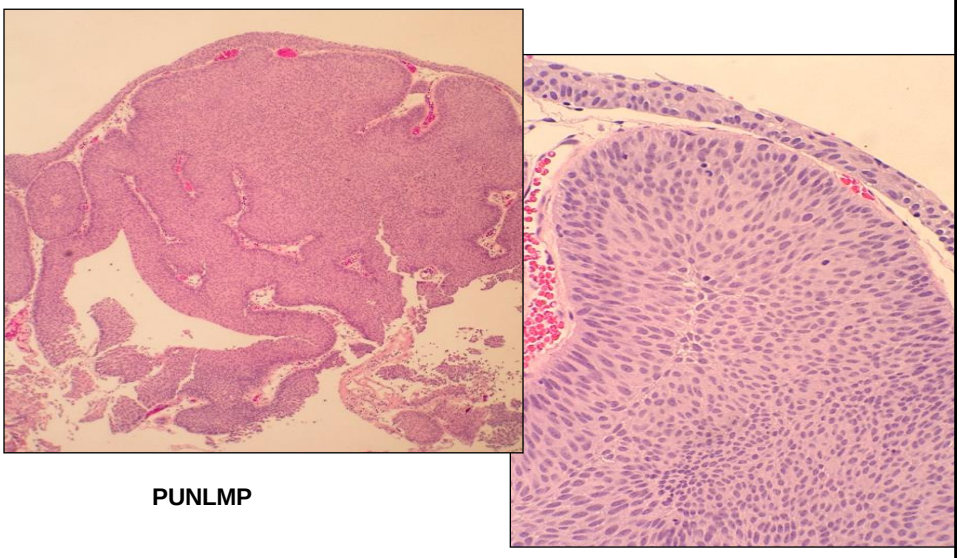
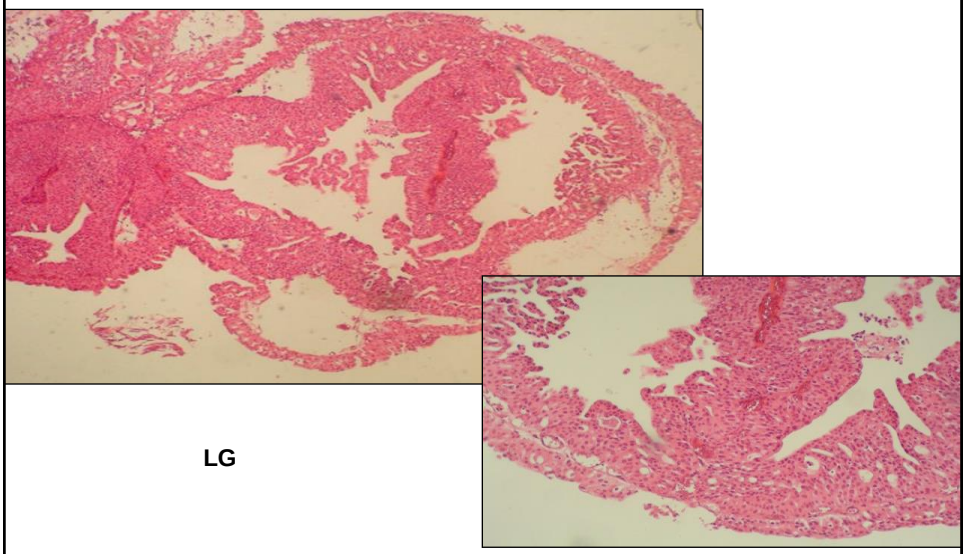

Ki-67 (%)
40
30
20
10
0
6
papilloma
26
TaLMP
34
TaLG
16
TaHG
Non-invasive tumors


Broad Front Invasion

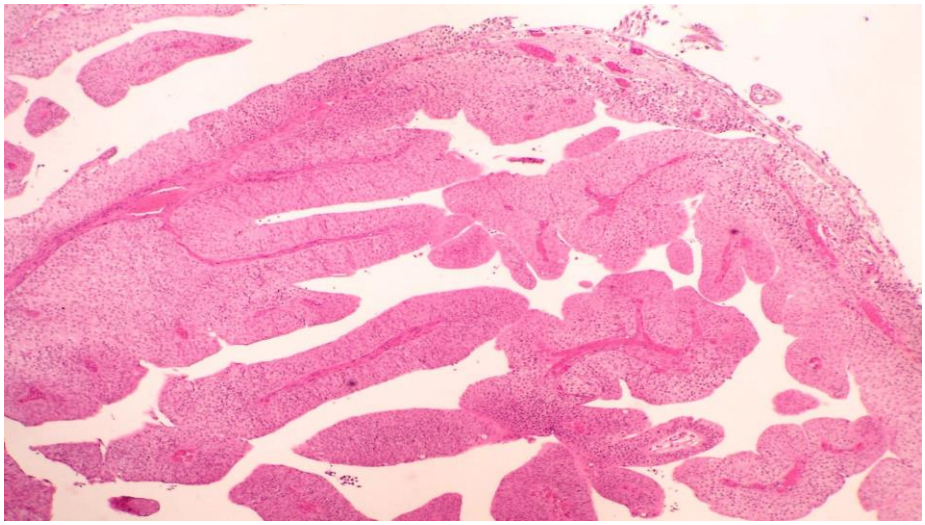

HG

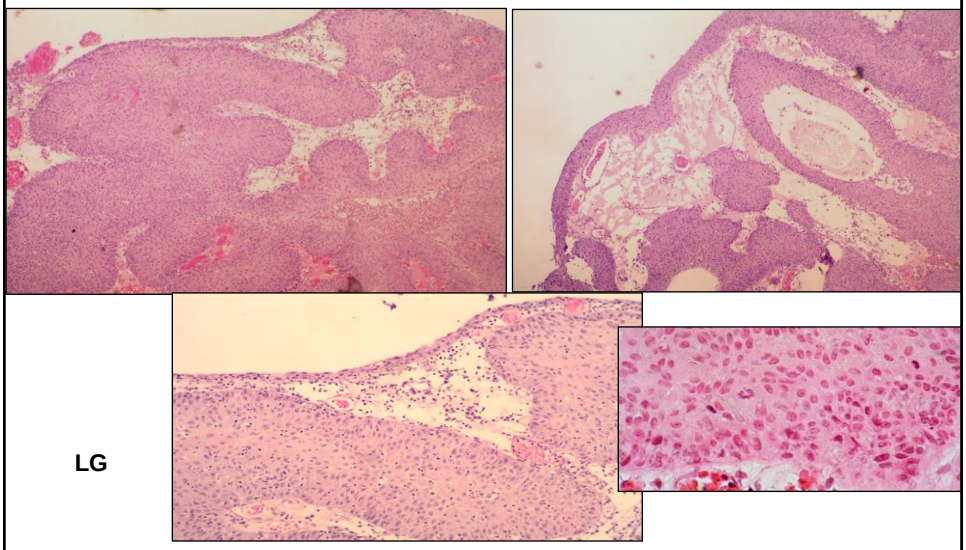


PUNLMP

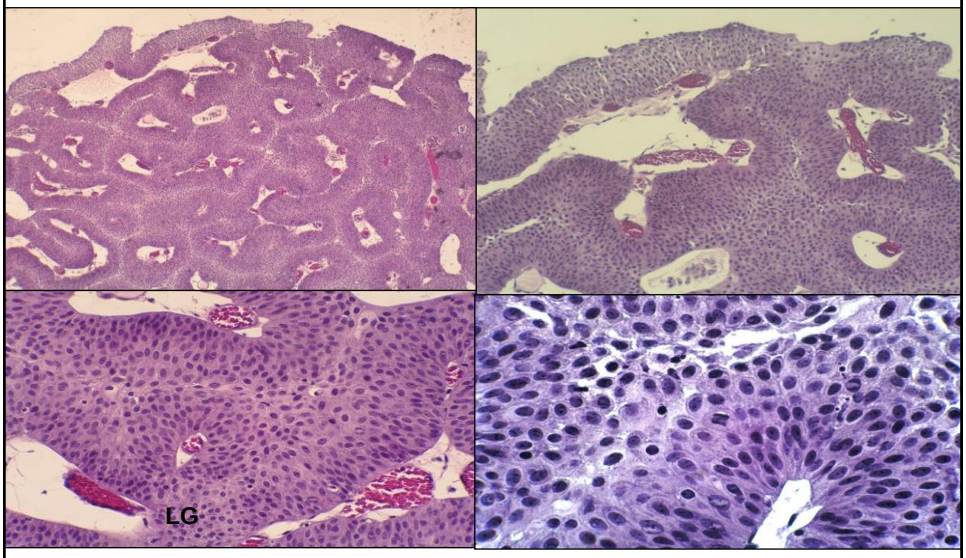


LG





LG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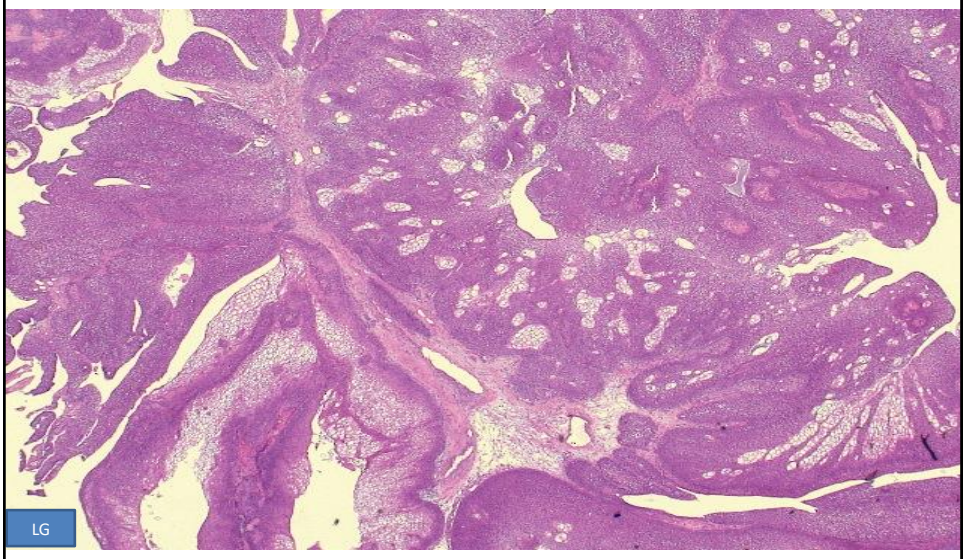
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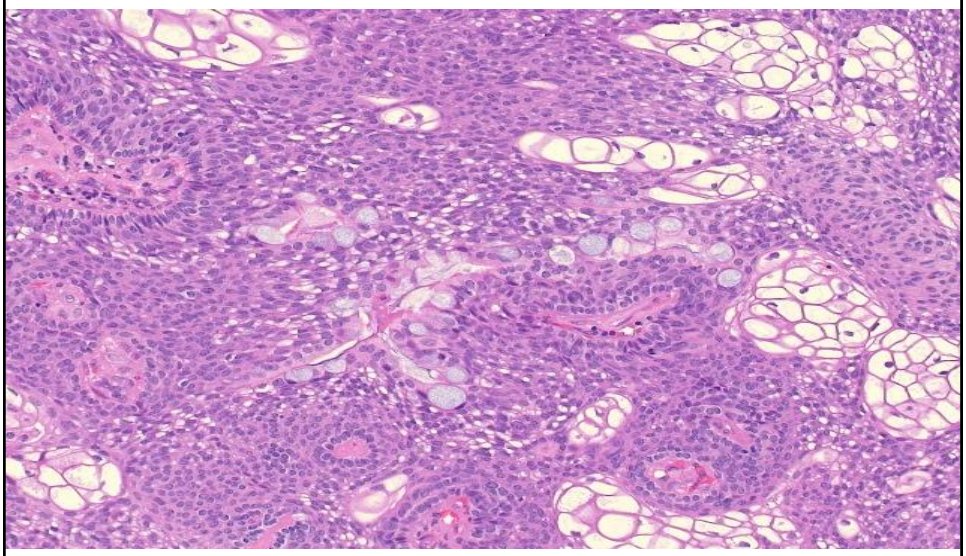

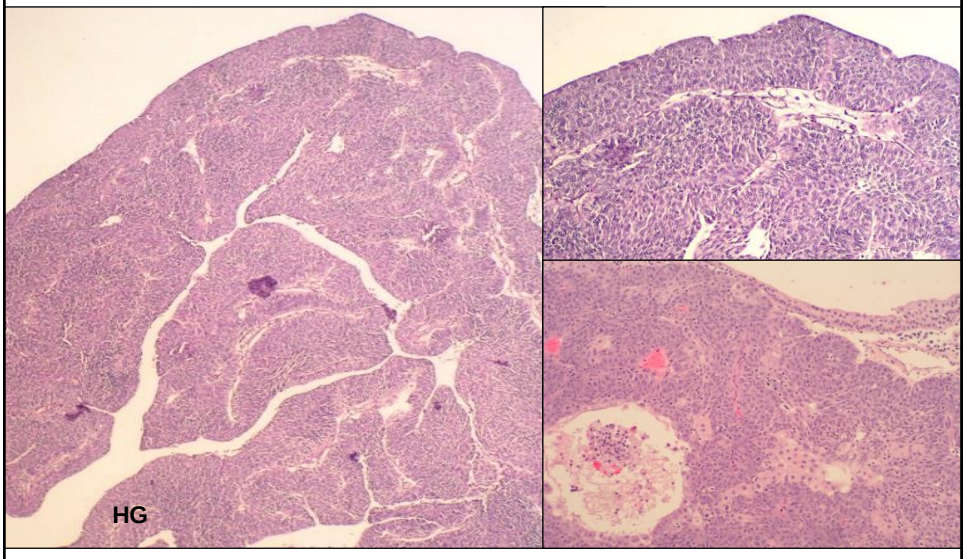
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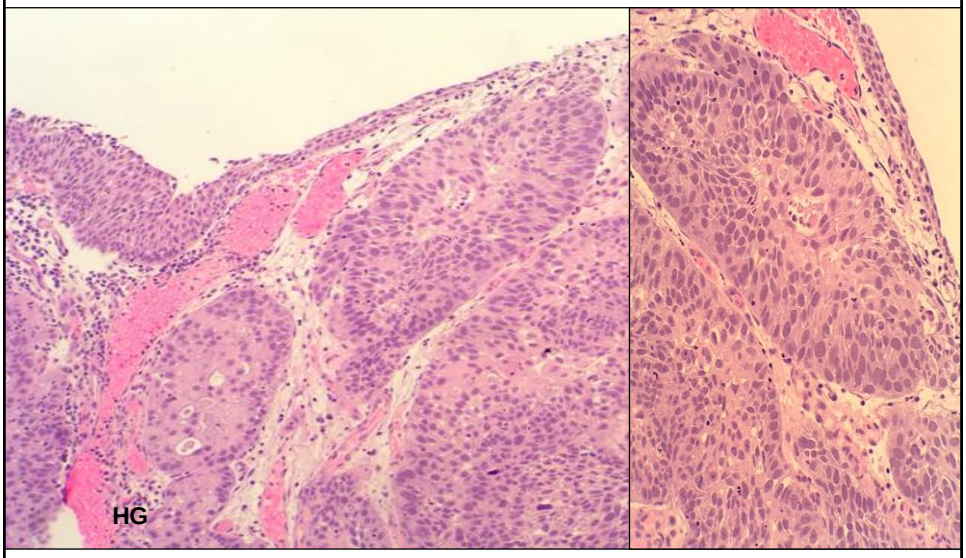
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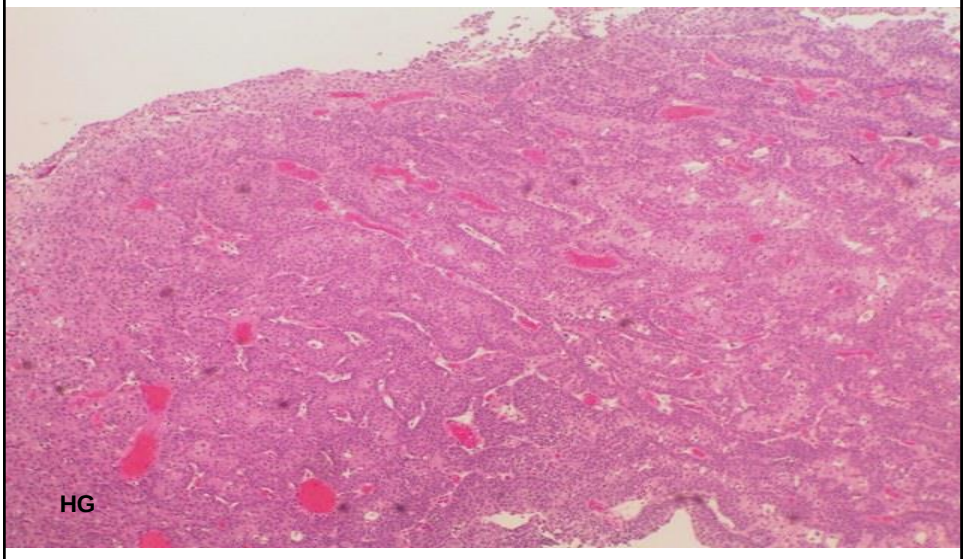
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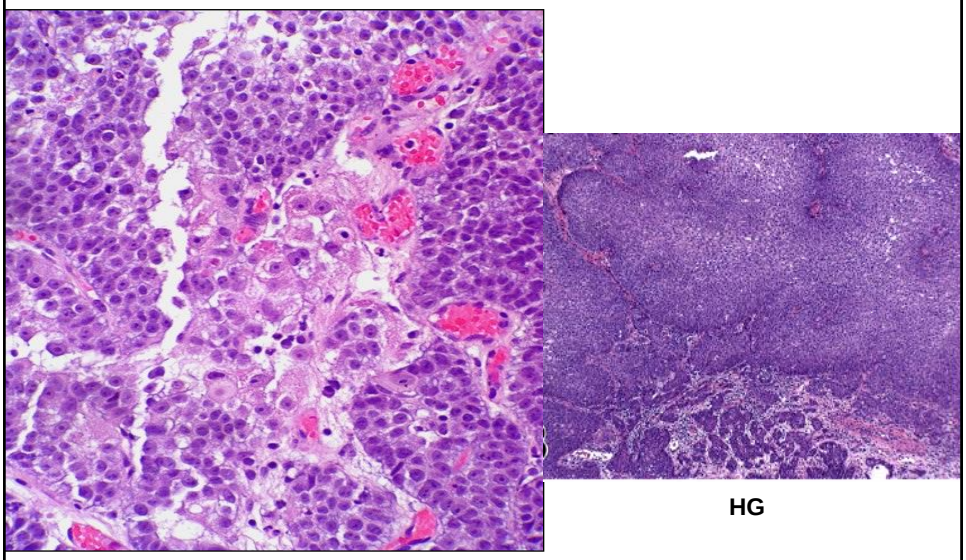


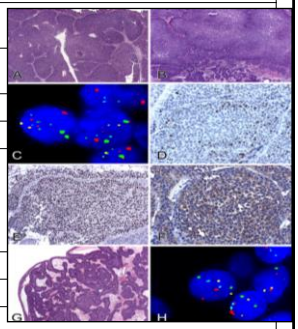
HG

Inverted Growth Patterns of Cancer

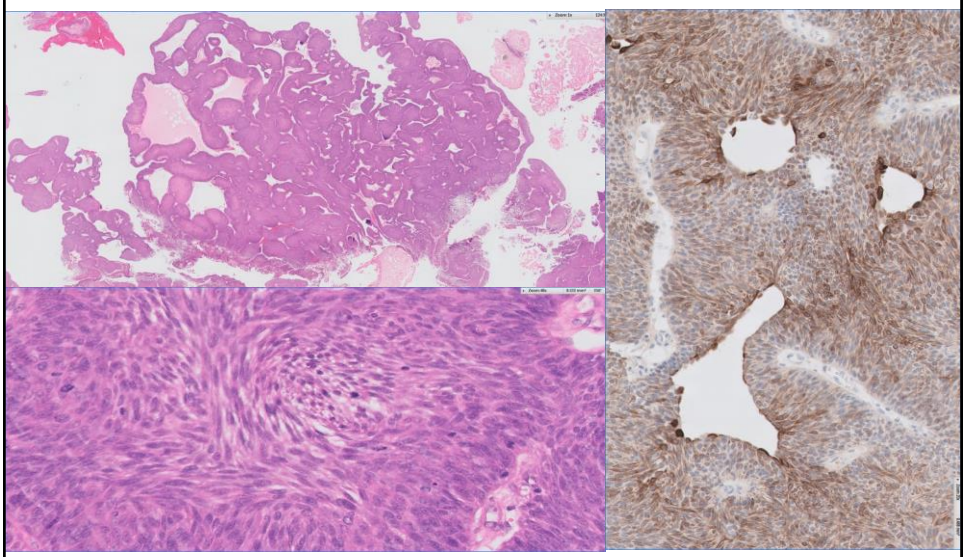
- **The diagnosis of invasion should be made when there are:**

- **Irregularities of the contours of the neoplastic nests**
- **Jagged edges**
- **Desmoplastic or inflammatory stroma surrounding these nests.**

	Inverted-Pattern Carcinoma	Inverted Papilloma
Cytologic Atypia / Tumor Grade[1]	Grade 1: 9/29 (31%) Grade 2: 14/29 (48%) Grade 3: 6/29 (21%)	0/15 (0%) with significant cytologic atypia
Coexisting exophytic papillary component	22/29 (76%)	0/15 (0%)
Coexisting flat urothelial dysplasia/CIS	0/29 (0%)	0/15 (0%)
Stromal invasion	12/29 (41%)	0/15 (0%)
Peripheral palisading	13/29 (45%)	15/15 (100%)
Mitotic activity: ● **< 1 / 10 HPF** ● **1-5 / 10 HPF** ● **5-15 / 10 HPF** ● **> 15 / 10 HPF**	 5/29 (17%) 16/29 (55%) 5/29 (17%) 3/29 (10%)	 12/15 (80%) 3/15 (20%) 0/15 (0%) 0/15 (0%)
Ki-67 immunoreactivity	19/29 (66%)[2]	0/15 (0%)
P53 immunoreactivity	17/29 (59%)[3]	1/15 (7%)
CK20 immunoreactivity	17/29 (59%)[4]	0/15 (0%)
UroVysion FISH positivity	21/29 (72%)	0/15 (0%)



Jones, Lopez-Beltran, Montironi, Cheng, AJSP, 2007



Histopathology

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Telomerase reverse transcriptase (TERT) promoter mutation analysis of benign, malignant and reactive urothelial lesions reveals a subpopulation of inverted papilloma with immortalizing genetic change

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Aims: To understand more clearly the genetic ontogeny of inverted papilloma of urinary bladder, we analysed telomerase reverse transcriptase (TERT) promoter mutation status in a group of 26 inverted papillomas in comparison with the mutation status of urothelial carcinoma with inverted growth (26 cases), conventional urothelial carcinoma (36 Ta non-invasive urothelial carcinoma, 35 T2 invasive urothelial carcinoma) and cystitis glandularis (25 cases).

Methods and results: TERT promoter mutations in inverted papilloma, urothelial carcinoma with inverted growth, urothelial carcinoma and cystitis glandularis were found in 15% (four of 26), 58% (15 of 26), 63% (45 of 71) and 0% (none of 25), respectively. C228T mutations were the predominant mutations (97%) found in bladder tumours, while C250T aberrations occurred in approximately 3% of bladder tumours. In the inverted papilloma group, TERT mutation occurred predominantly in female patients ($P = 0.006$). Among urothelial carcinomas, TERT promoter mutation status did not correlate with gender, histological grade or pathological stage.

Conclusions: TERT promoter mutations were found in 15% of inverted papillomas. Our data suggest that there is a subpopulation of inverted papilloma that shares a carcinogenetic pathway with urothelial carcinoma with inverted growth and conventional urothelial carcinomas. Caution is warranted in exploring TERT promoter mutation status as a screening or adjunct diagnostic test for bladder cancer.