VGO NORTE INTERNATIONAL GU DEBATES

Variant histologies in MIBC: Which ones, how often and how much should conditions my preoperative treatment selection?

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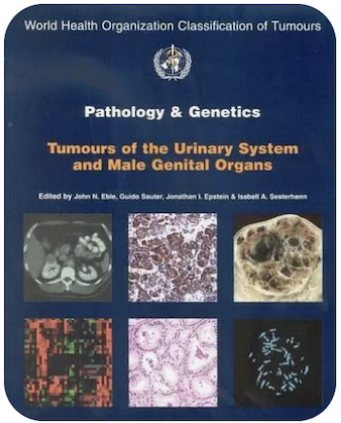
8th October 2026

I have no conflicts of interest

Contents:

- OMS Classifications
- What causes biological diversity and how it is classified
- Molecular subtypes
- What is the clinical relevance of histological typing
- How can pathology contribute to precision medicine
- Conclusions

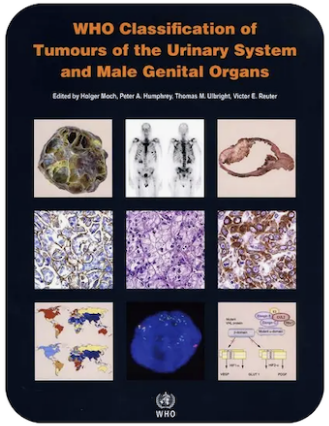
WHO 2004



Infiltrating urothelial carcinoma
- With squamous differentiation
- With glandular differentiation
- With Trophoblastic differentiation

- Nested
- Microcystic
- Micropapillary
- Limphoepithelioma-like
- Lymphoma-like
- Plasmocytoid
- Sarcomatoid
- Giant cell
- Undifferentiated

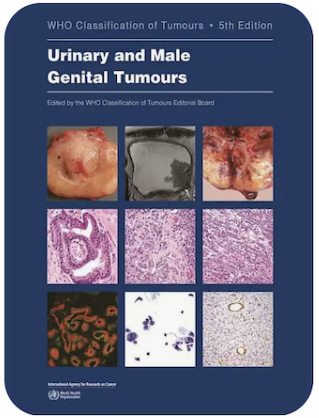
WHO 2016



Infiltrating urothelial carcinoma
- With squamous differentiation
- With glandular differentiation
- With Trophoblastic differentiation
- Small cell

- Nested, including large
- Microcystic
- Micropapillary
- Limphoepithelioma-like
- Plasmocytoid/Signet ring cell/diffuse
- Sarcomatoid
- Giant cell
- Clear cell
- Poorly differentiated

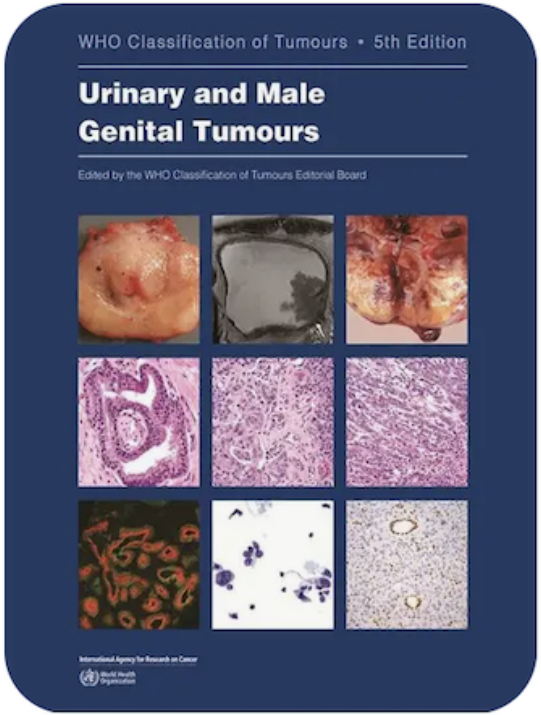
WHO 2022



Invasive urothelial carcinoma
- UC with squamous differentiation
- UC with glandular differentiation
- UC with Trophoblastic differentiation
- UC with Müllerian differentiation

- Nested UC
- Large nested UC
- Tubular and microcystic UC
- Micropapillary UC
- Limphoepithelioma-like UC
- Plasmocytoid UC
- Giant cell UC
- Lipid-rich UC
- Clear cell (glycogen-rich) UC
- Sarcomatoid UC
- Poorly differentiated UC

WHO 2022 Classification

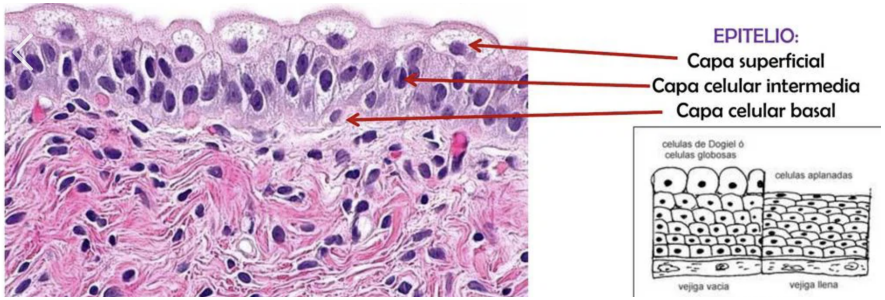


- Term “variant” has been replace by “subtypes”
- Subtype vs divergent differentiation
- Divergent differentiation: different line of epithelial origin
  - Squamous
  - Glandular
  - Trophoblastic
  - Müllerian
- Subtype: urothelial cells but morphology (and IHQ) is different
- Mixture of subtype and divergent differentiation not uncommon

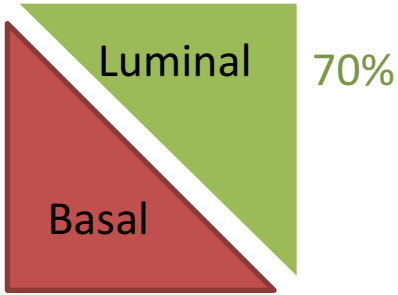
→ List and quantify in our report

UROTHELIUM

HE stain



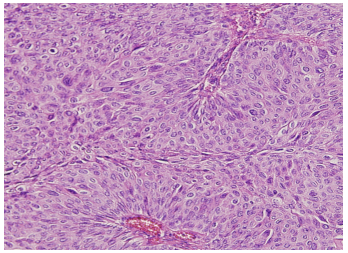
Cell characteristic



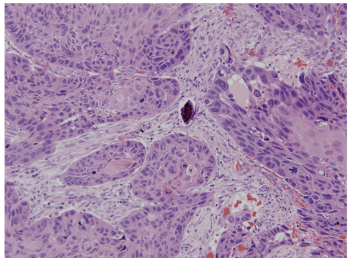
70%

30%

Luminal



PPARG
ESR1
FGFR3

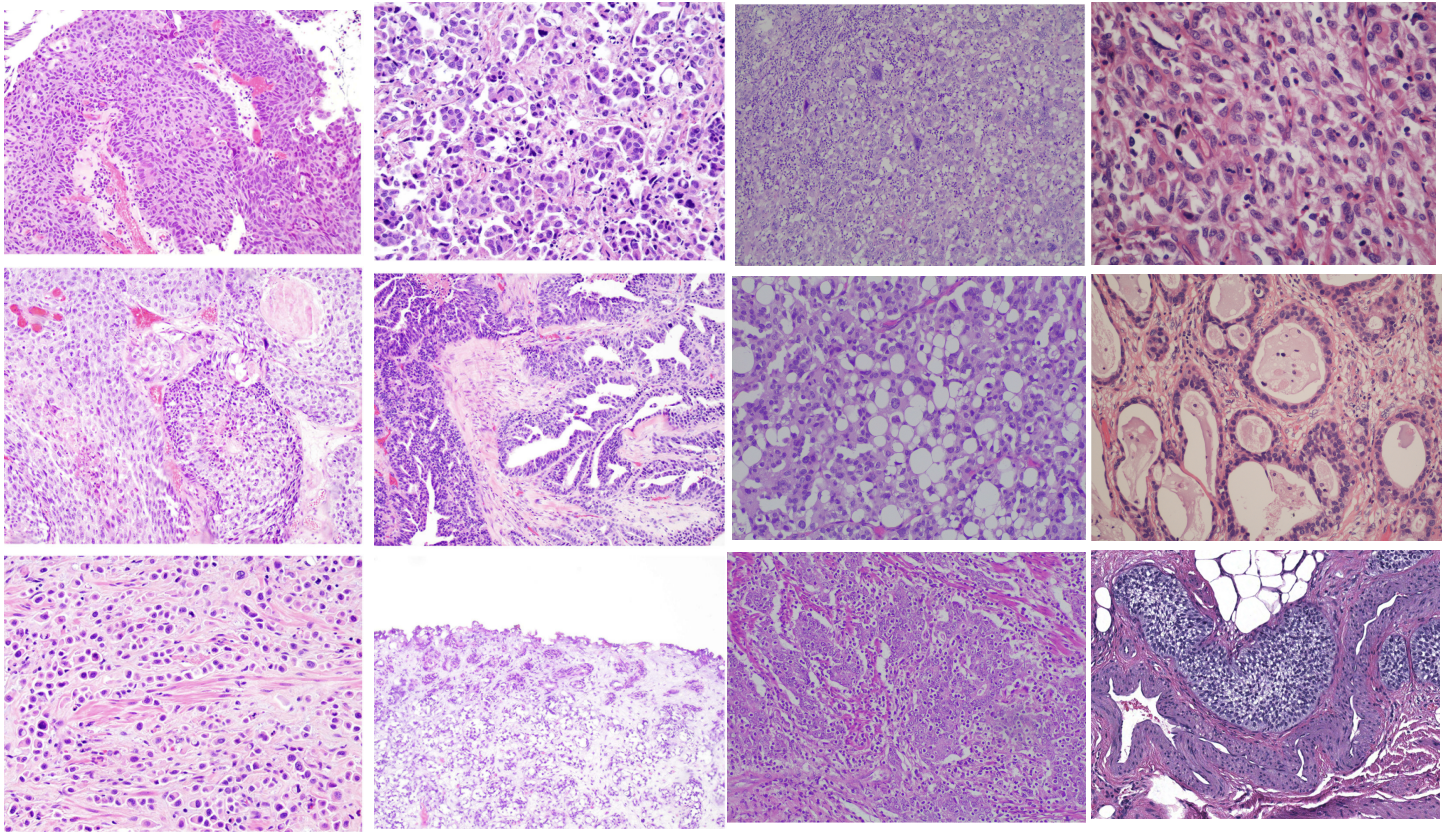


TP63
STAT3
EFGR

Basal

What causes biological diversity and how it is classified





Appl Immunohistochem Mol Morphol . 2021;29 (8): 619-625; OMS, 2022

What is the clinical relevance of histological typing

Micropapillary (MP) subtype

- Account uo to 6% of urothelial carcinoma
- Commonly admixed with convectional carcinoma
- Cis present in 50% cases
- Male predominance
- Frecuently presents at high stage
- LVI very common

Table 3. Clinicopathological features of patients (studies with $n \geq 50$) who underwent RC for MPUC

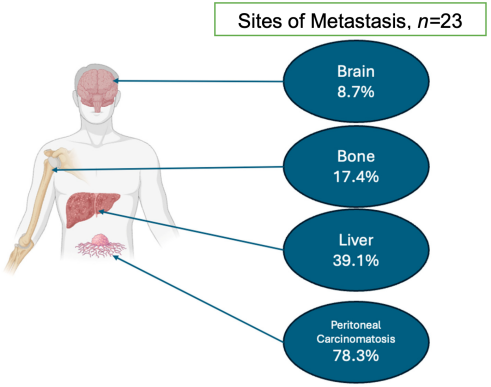
Study (first author, year)	N	Clinicopathological features, n (%)					
		Males	NAC	pT≤1	pT2	≥pT3	pN+
Compérat (2010) [21]	57	62 (86)	NR	12 (21)	7 (12)	38 (67)	25 (44)
Wang (2012) [40]	73	62 (85)	3 (4)	10 (14)	15 (21)	48 (66)	37 (51)
Cai (2014) [41]	54	NR	NR	8 (15)	32 (59)	14 (26)	11 (20)
Moschini (2017) [3]	89	79 (89)	2 (2)	NR	NR	48 (54)	36 (40)
Sui (2016) [11]	380	300 (79)	31 (8)	71 (19)	85 (22)	224 (59)	206 (54)
Fernández (2017) [16]	103	64 (86)	0 (0)	31 (42)	8 (11)	34 (47)	32 (45)
Mendiratta (2018) [25]	82	69 (84)	19 (23)	12 (14)	7 (9)	63 (77)	NR
Pooled results, % (95% CI)	838	84 (80–87)	–	20 (14–28)	21 (11–32)	57 (46–67)	43 (33–52

Eur Urol 2019; 75 (4): 649-658

MP> 30% predicts nodal metastasis at cistectomy

Plasmocytoid subtype

- Commonly admixed with convectional carcinoma
- Typically present at advance stage
- Frequently positive margins at cystectomy
- High risk of peritoneal spread
- High rates of recurrence and death from the disease



Cancers 2024,16, 3050

Peritoneal carcinomatosis 78%

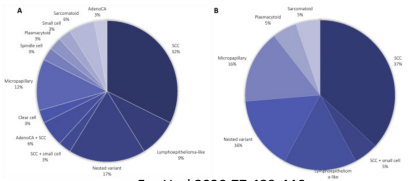
LE-Like subtype

- Resembles LE of the pharynx
- More comments in males in late adulthood
- Can be pure or mixed
- If pure favorable prognosis
- Rare, largest series of 34 cases

Table 3 Outcomes for LELC types and treatment modalities

LELC Type	Cases	NED	*p*-value	DOD	*p*-value
Pure	62	71.0%	0.00002	1.6%	0.0001
Predominant	36	75.0%	0.00002	5.6%	0.002
Mixed	38	31.6%	-	28.9%	-
Treatment	Cases	NED	*p*-value	DOD	*p*-value
MM	112	67.9%	0.002	7.1%	0.04
RC+	59	67.8%	0.002	10.2%	0.08
PC+	8	50.0%	0.21	12.5%	0.22
TURBT+	45	71.1%	0.002	2.2%	0.012
TURBT−	21	33.3%	-	23.8%	-

BMC Urology (2017) 17:34

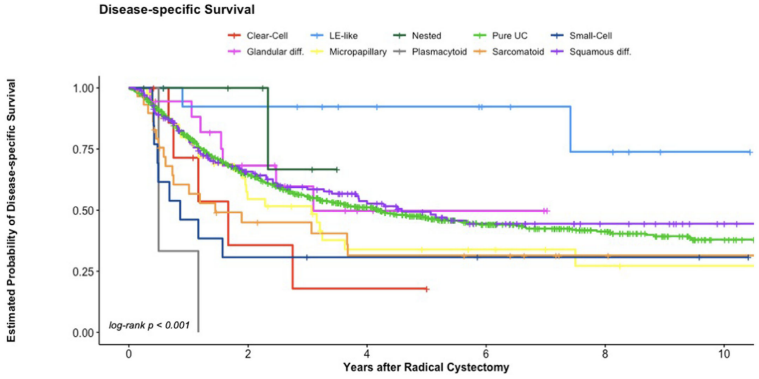


Eur Urol 2020;77:439-446

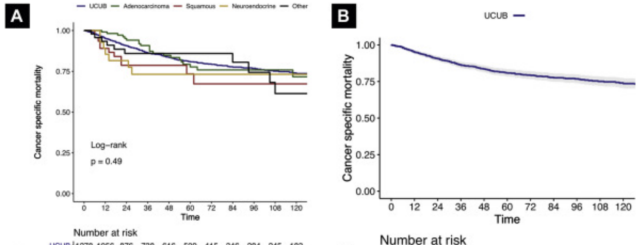
Neoadyuvant ICI: 2/3 LEL carcinomas were ypT0 at cystectomy

Good response to platinum chemotherapy (pure)

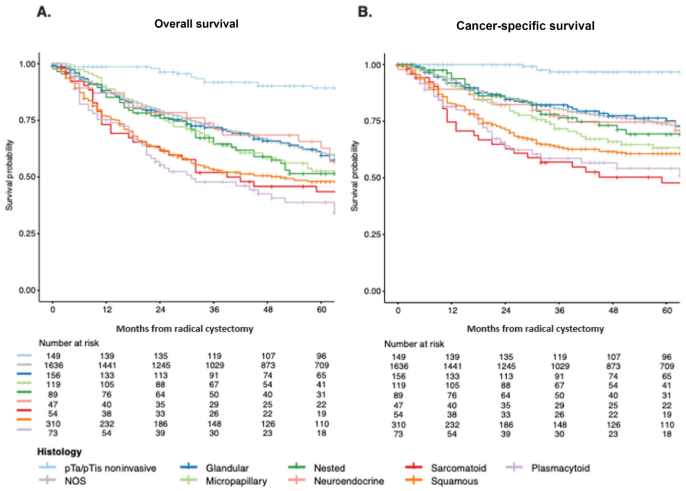
What is the clinical relevance of histological typing



BJU Int 2023; 132: 170–180



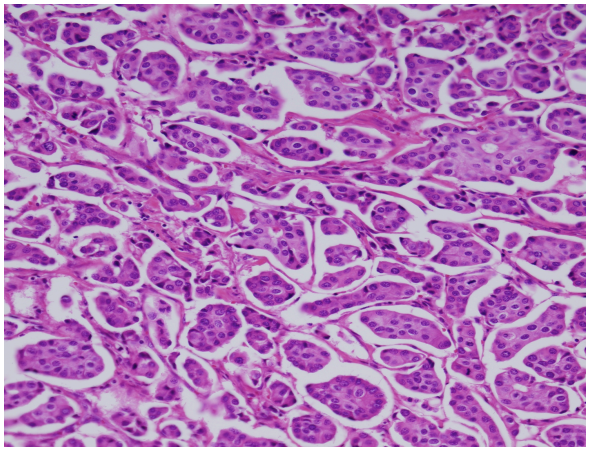
Clin Genitourin Cancer 2020; 18:117-128

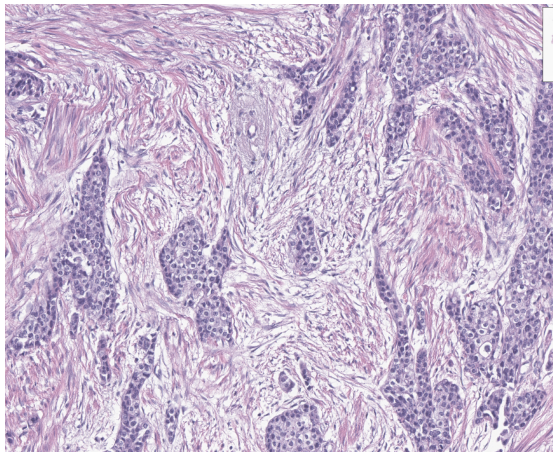


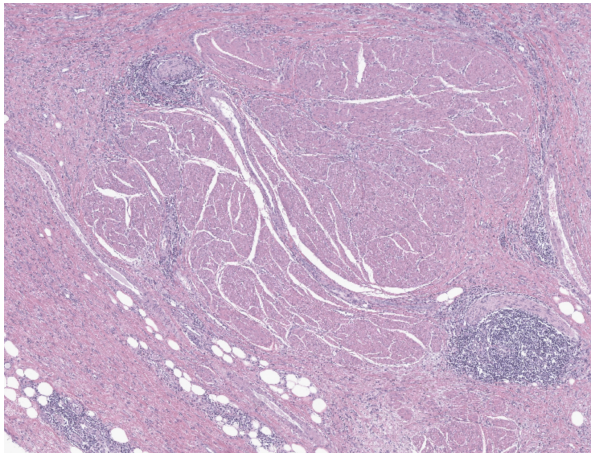
Eur Urol 2025;88:472-481

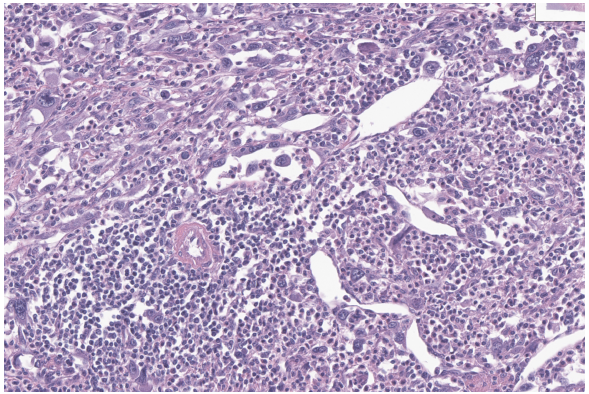
Identification of subtypes is an important part of risk stratification, diagnostic component, prognostic and therapeutic implications

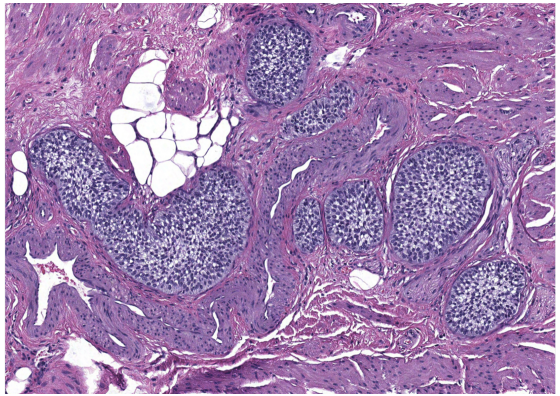
What causes biological diversity and how it is classified

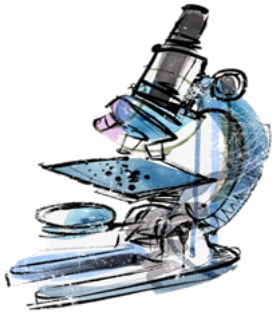




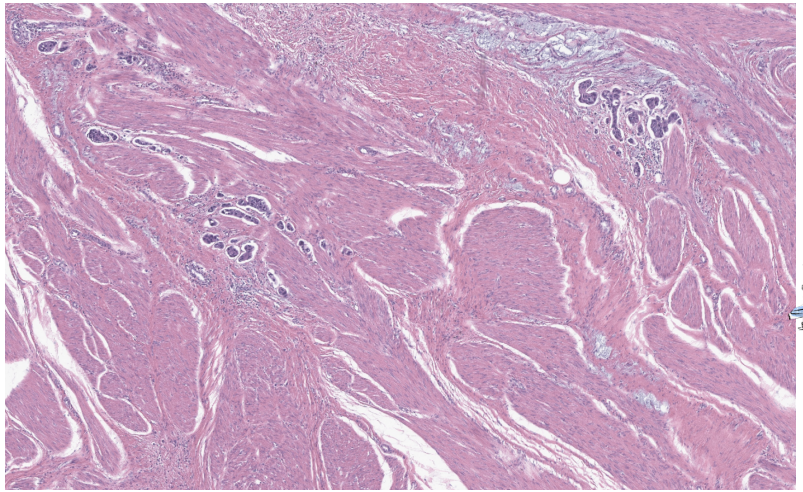


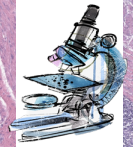


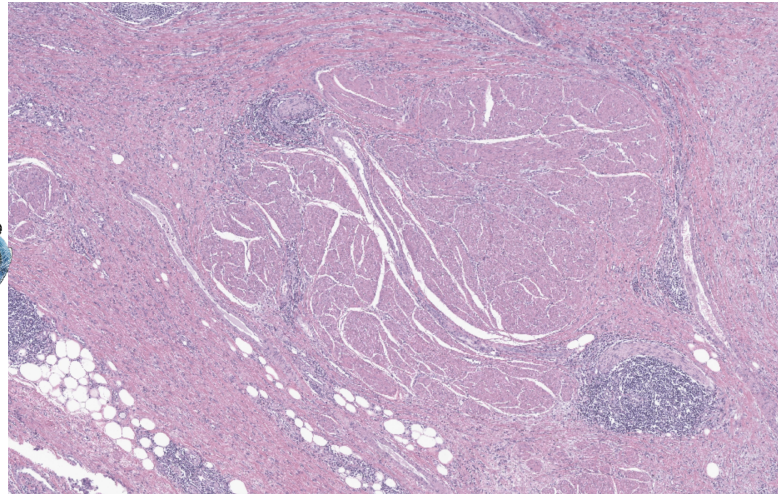




What causes biological diversity and how it is classified



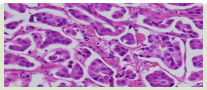
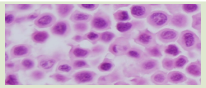
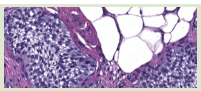
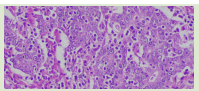
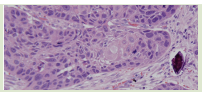
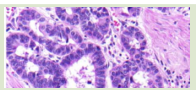
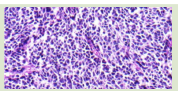




The presence of TLS-like lymphocyte aggregates observed on routinely used hematoxylin and eosin-stained slides of RC specimens may be an important predictor of survival outcomes after RC.

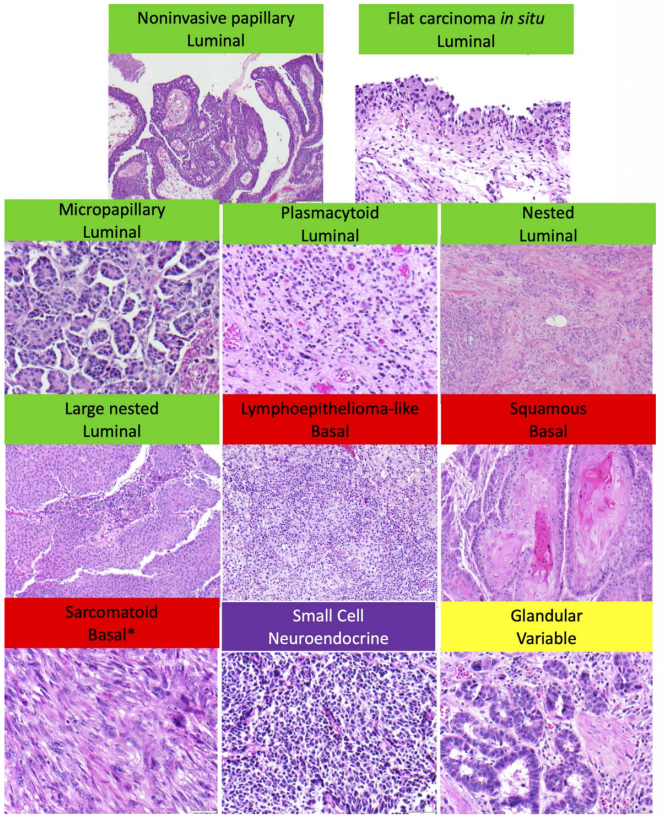
Oncol Res. 2026;34(7):25; Int J Urol 2026 Mar;33(3):e70392; Curr Urol Rep. 2025 Dec 29;27(1):3.

Identification of subtypes is an important part of risk stratification-diagnostic component, prognosis and therapeutic implications

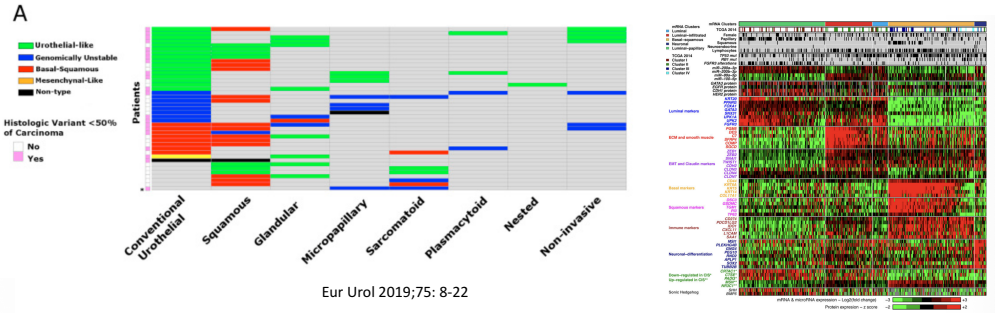
Histology	Micropapillary	Plasmocitoid	Nested	LELC	Squamous	Glandular	Neuroendocrine
							
Molecular subtype	Luminal	Luminal	Luminal	Basal	Basal	Luminal	NE-like
Specific Genetics	ERBB2/HER2	CDH1 PIK3CA	FGFR3 TSC1	PD-L1 high Inmune infiltrates	PTEN/PIK3CA	TERT/PTEN	TP53, RB1, PTEN
Clinical Prognosis	Adverse frequent LVI	Adverse peritoneal	Higher stage	Good	Higher stage female		Adverse
Treatment	Early cystectomy Chemo more effective T3/T4, M+	Early cystectomy	Cystectomy	Chemosensitive	Cystectomy	Cystectomy	Cystectomy Chemotherapy
Targeted Therapy	ADC-HER2 status		FGFR3 inhibitor	Inmune chechpoint inhibitor			DLL3 emerging target

Modified from, M. Downes ECP 2025. OMS, 2022

What causes biological diversity and how it is classified

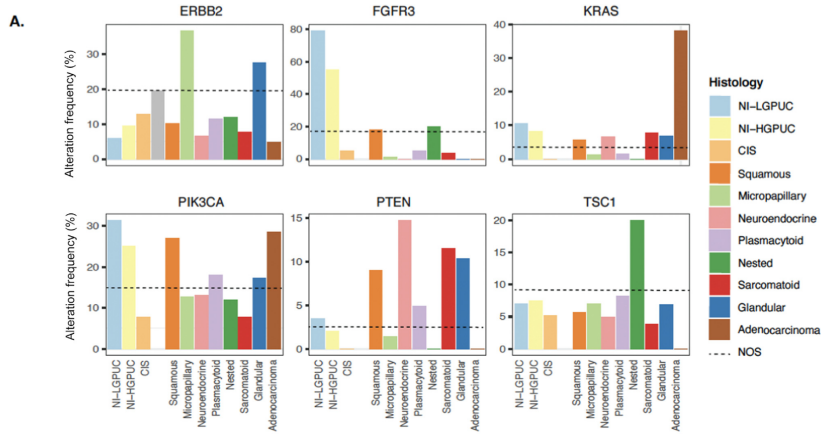


Adv Anat Pathol 2024;31:178–187)



Eur Urol 2019;75: 8-22

Cell . 2017 October 19; 171(3): 540–556.e25.

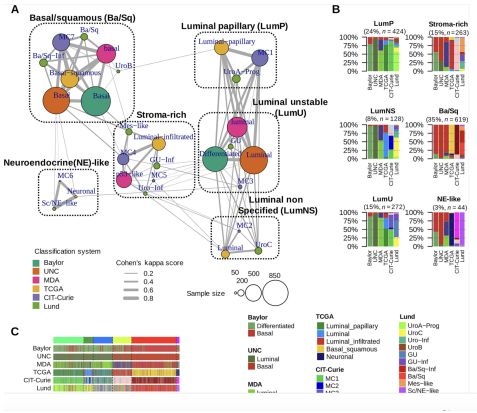


Eur Urol 2025;75:472-481

Molecular subtypes

% of MIBC	24%	8%	15%	15%	35%	3%
Class Name	Luminal Papillary (LumP)	Luminal Non-Specified (LumNS)	Luminal Unstable (LumU)	Stroma-rich	Basal/Squamous (Ba/Sq)	Neuroendocrine-like (NE-like)
Differentiation	Urothelial / Luminal				Basal	Neuroendocrine
Oncogenic mechanisms	FGFR3 + PPARG + CDKN2A -	PPARG +	PPARG + E2F3 +, ERBB2 + Genomic instability Cell cycle +		EGFR +	TP53 -, RB1 -, Cell cycle +
Mutations	*FGFR3* (40%), *KDM6A* (38%)	*ELF3* (35%)	*TP53* (76%), *ERCC2* (22%) TMB +, APOBEC +		*TP53* (61%), *RB1* (25%)	*TP53* (94%) *RB1* (39%)*
Stromal infiltrate		Fibroblasts		Smooth muscle Fibroblasts Myofibroblasts	Fibroblasts Myofibroblasts	
Immune infiltrate				B cells	CD8 T cells NK cells	
Histology	Papillary morphology (59%)	Micropapillary variant (36%)			Squamous differentiation (42%)	Neuroendocrine differentiation (72%)
Clinical	T2 stage +	Older patients + (80+)			Women + T3/T4 stage +	
Median overall survival (years)	4	1.8	2.9	3.8	1.2	1

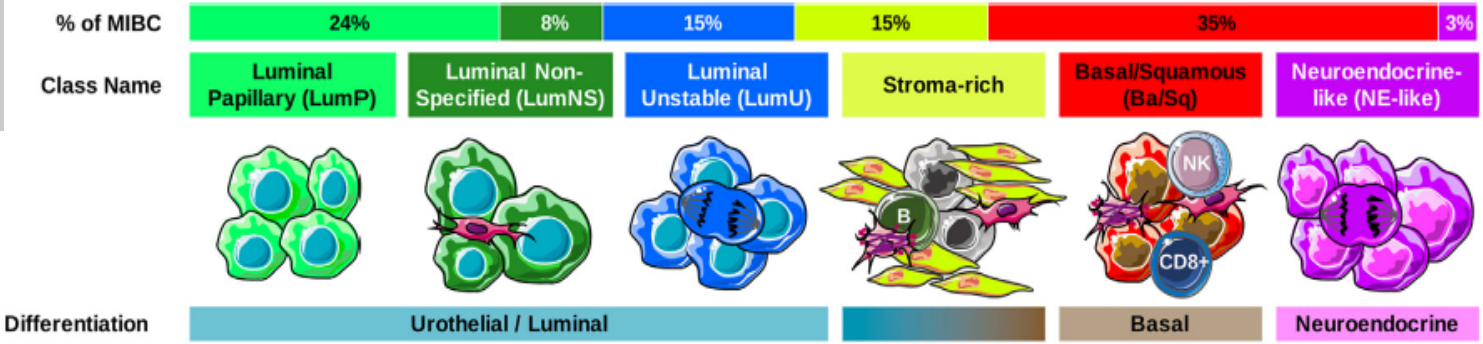
* 94% of these tumors present either RB1 mutation or deletion



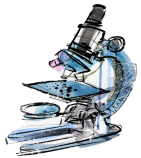
Eur Urol 2020;77:420-433

Molecular Classiffication 2020





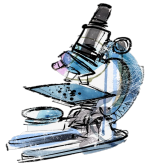
Histological Subtypes WHO 2022



Urothelial histologies 70%		Divergent histologies 30%
Conventional (80%) Micropapillary Nested Large nested Tubular/Microcystic Plasmocytoid	Lipid-rich UC Clear cell (glycogen-rich)* Sarcomatoid* Lymphoepitelioma like* Poorly differentiated	**Squamous** (90%) Throphoblastic Glandular Müller

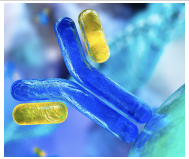
Molecular subtypes

Histological Subtypes WHO 2022



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Biomarkers



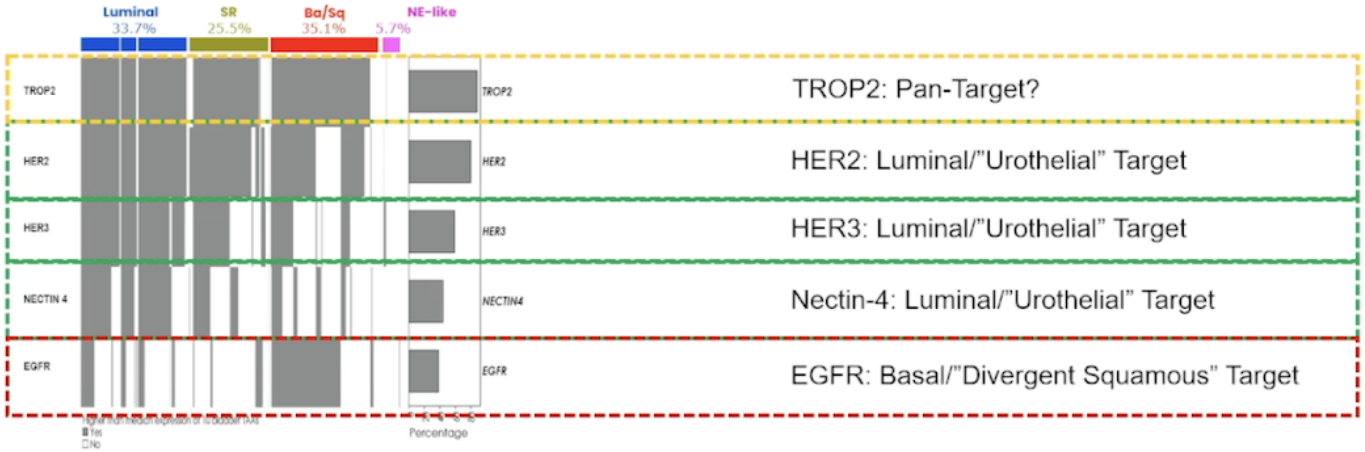
Nectin-4

PD-L1
EGFR

FGFR3
HER2-3

TROP2 Pan-target?

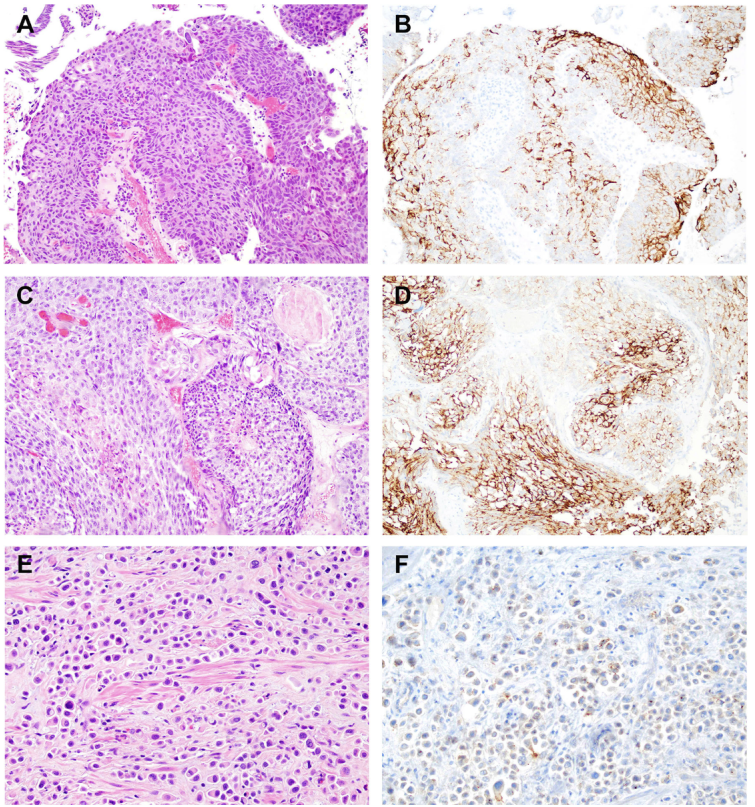
Modified from Ekstein M, ECP 2026; Kamoun A, et al. Eur Urol. 2020;77(4):420-433; Amin MB, et al. Mod . 2009;22 Suppl 2:596; Downes MR. In: Barber N, Ali A, editors. Urologic Cancers. Brisbane (AU): Exon; Publications;2022 Sep 12. Chapter 1



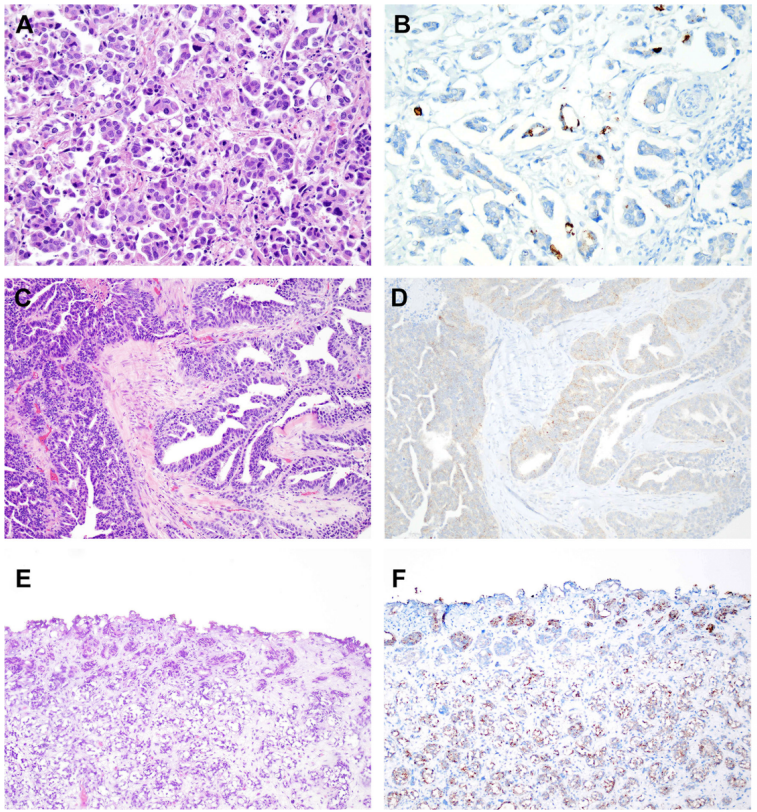
J Clin Oncol, 2025;43 (S Suppl): Abstract 828

Histology give us context but profiling targets adds solutions

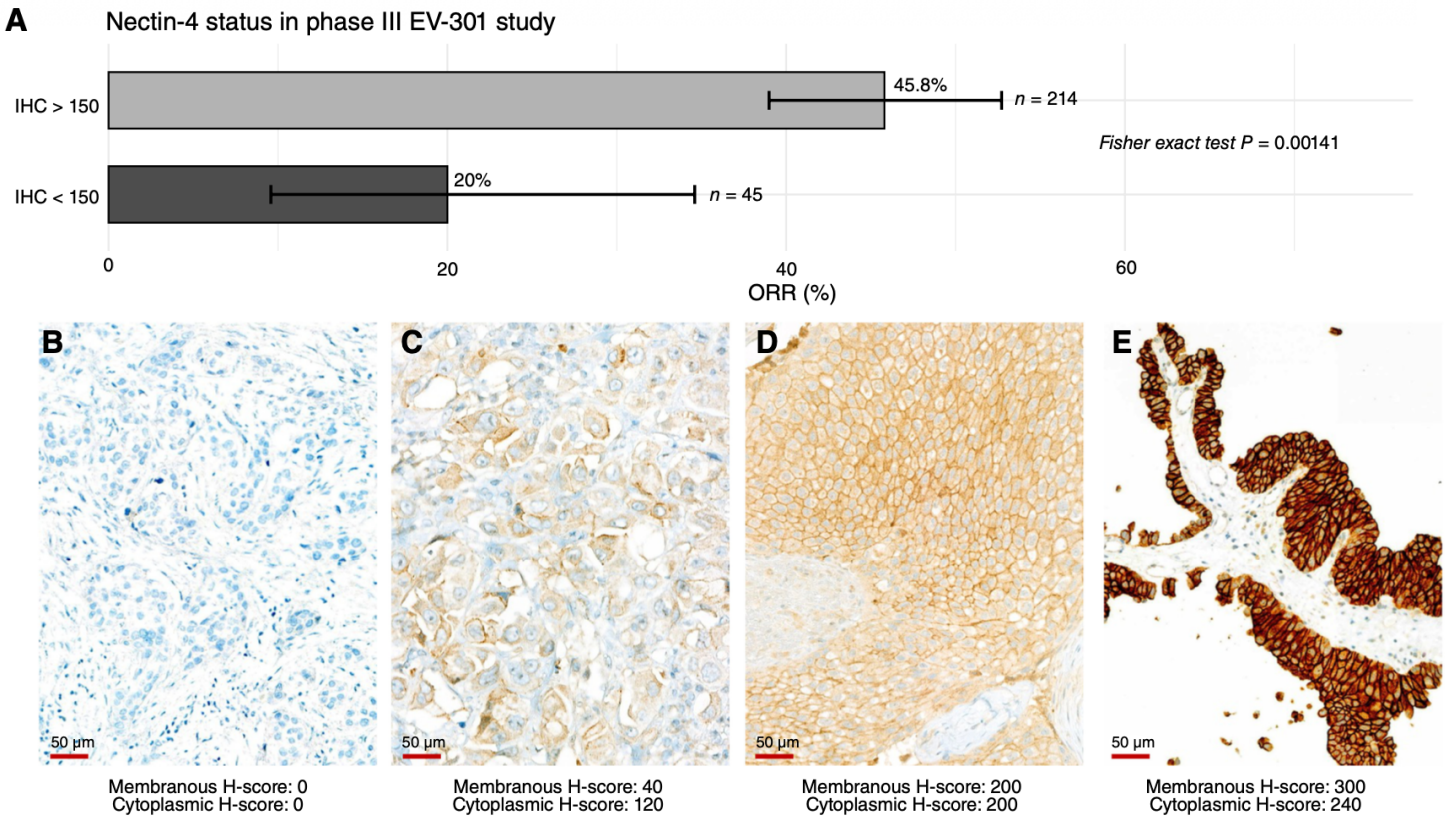
Nectin-4



Nectin-4



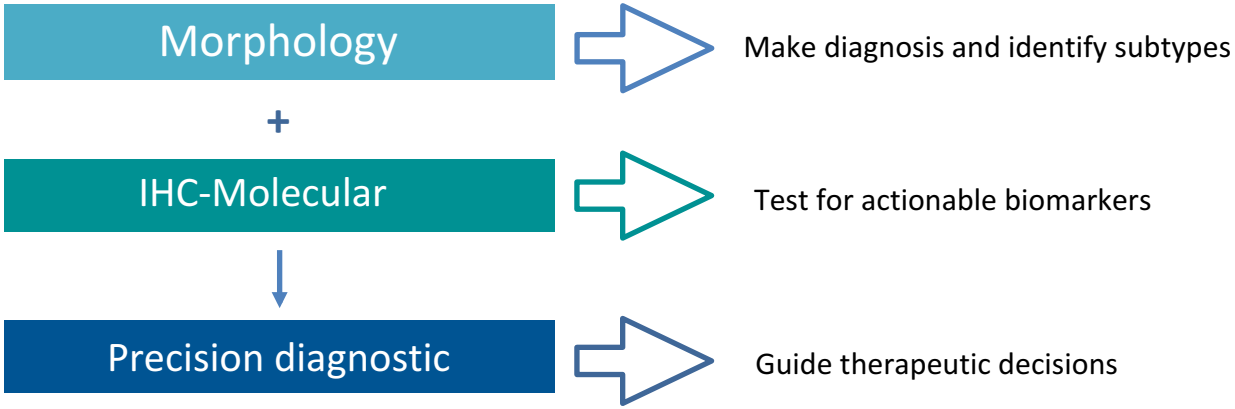
Appl Immunohistochem Mol Morphol 2021;29(8):619-625



Nectin4 Scoring System Predicts Enfortumab Vedotin Response

ASCO GU Cancers Symposium 2026, Poster 8, Abstract 854; Clin Cancer Res; 2026 Sep 9

Conclusions



Pathologist integrates diagnostic tools for precise therapy

Precise oncology demands precise diagnosis