Genomic and tumour characterisation of UTUC

Pr Eva Compérat

Dpt Pathology

Vienna/Paris

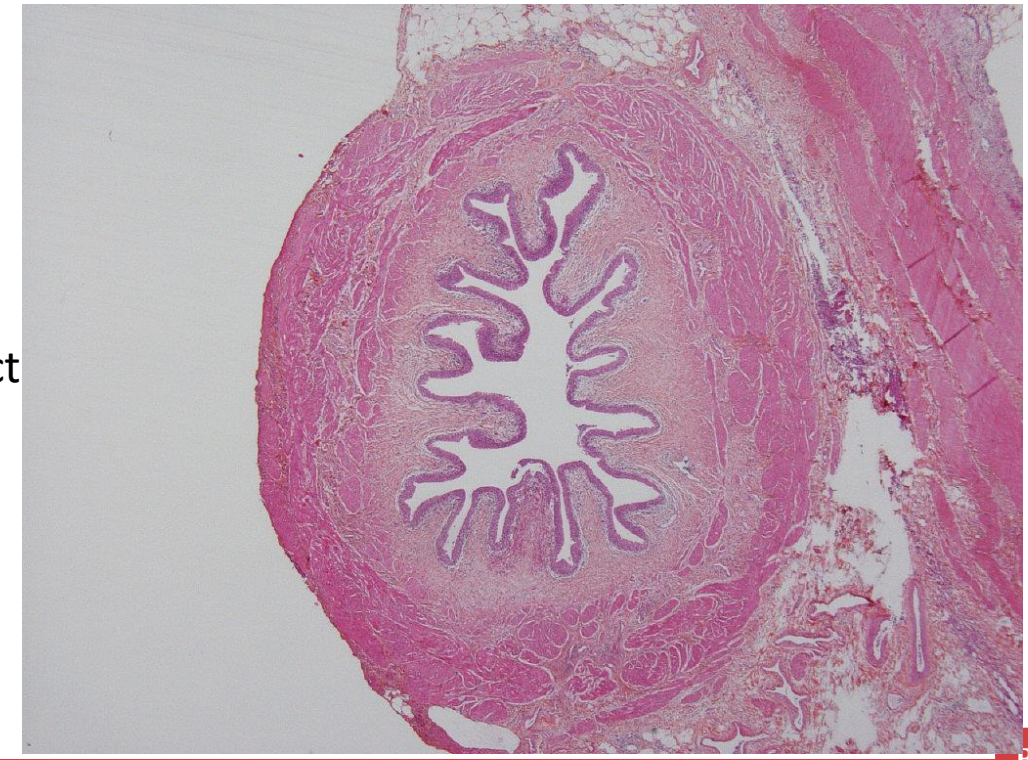
Conflicts of interest

Type of affiliation / financial interest	Name of commercial company
Receipt of grants/research supports	
Receipt of honoraria or consultation fees	Jansen, BMS
Stock shareholder	
Other support (please specify):	

From a histological point of view

- Globally same classification
- Same subtypes
- Staging +/- same

Same aspect



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- Same subtypes
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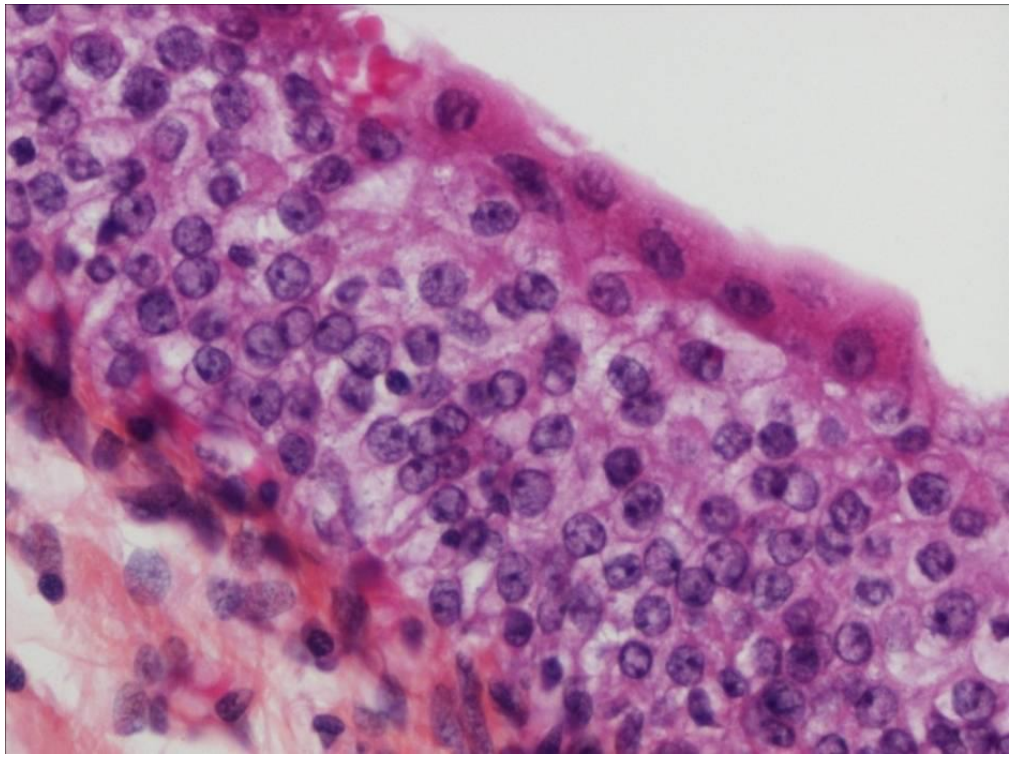
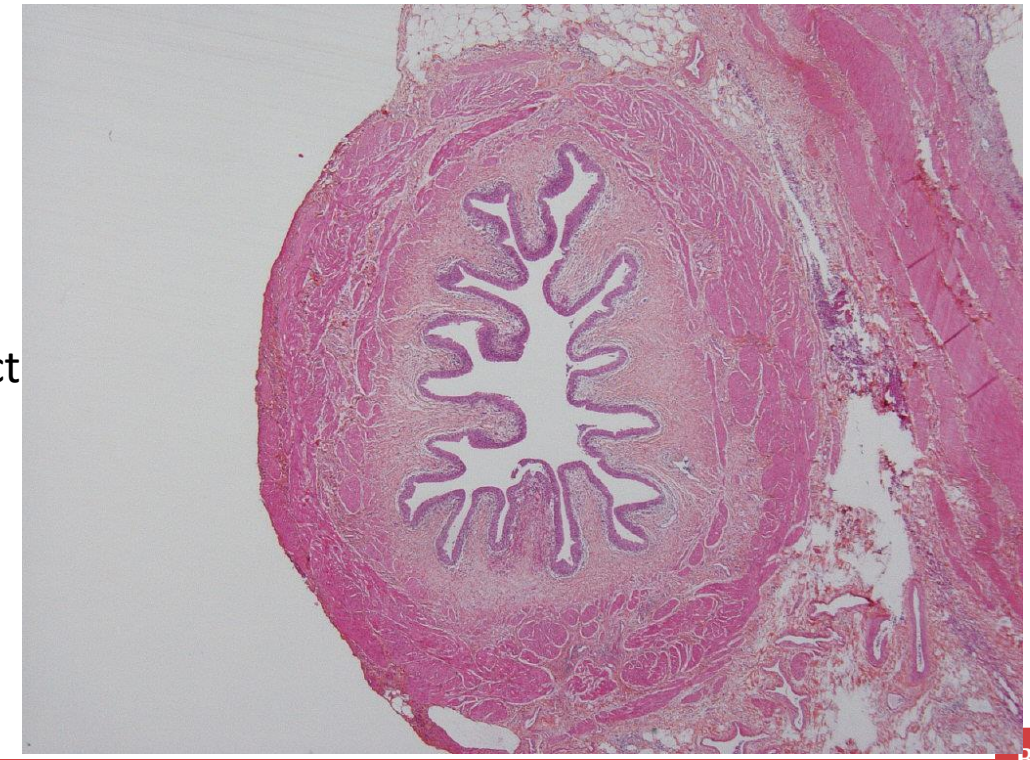


Same aspect



Histopathology

- Frequent
  - Squamous differentaition
  - Inverted lesions
  - Invasiveness tricky+++

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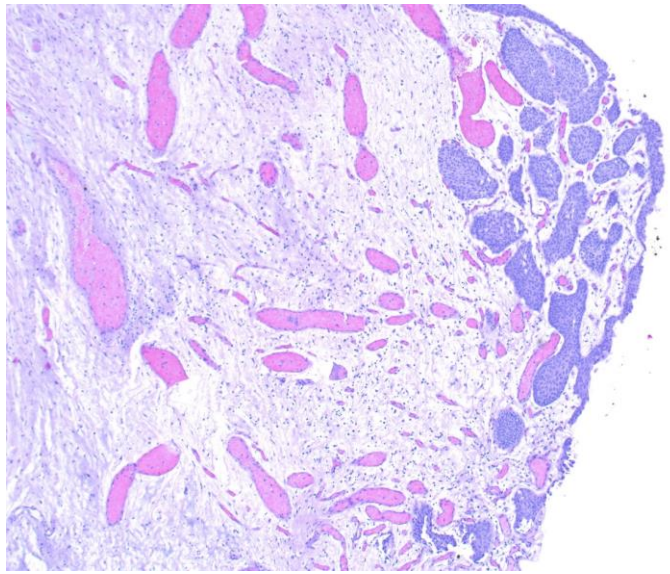
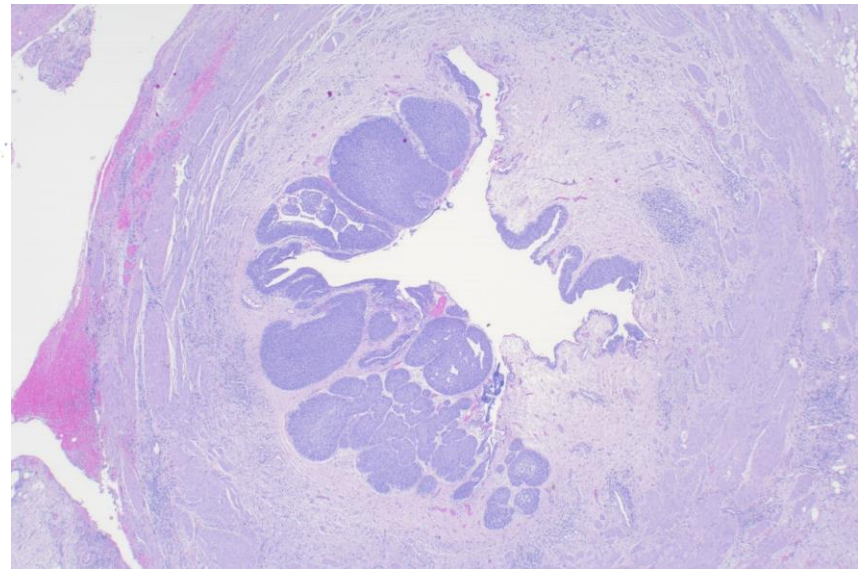
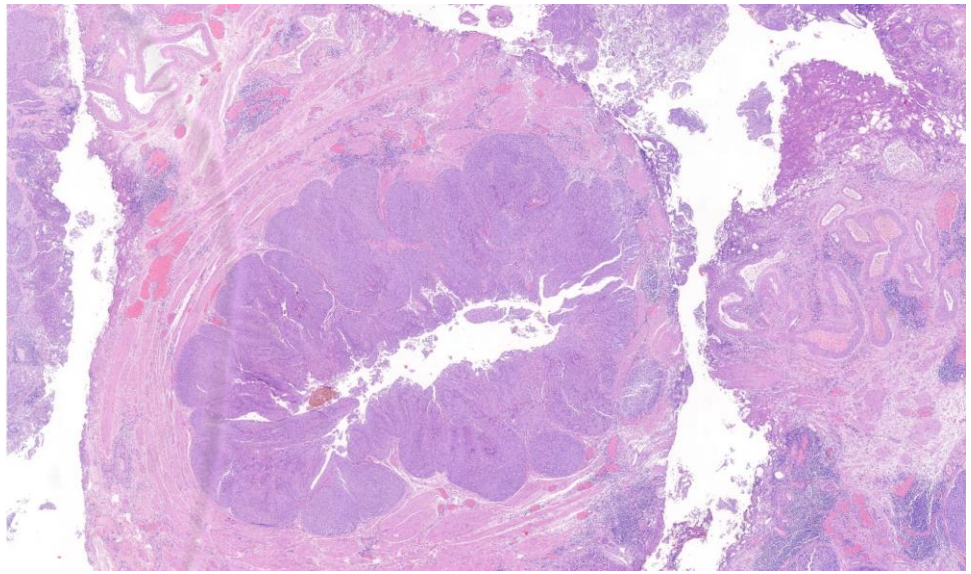






Prognostic factors and predictive tools for upper tract urothelial carcinoma: a systematic review

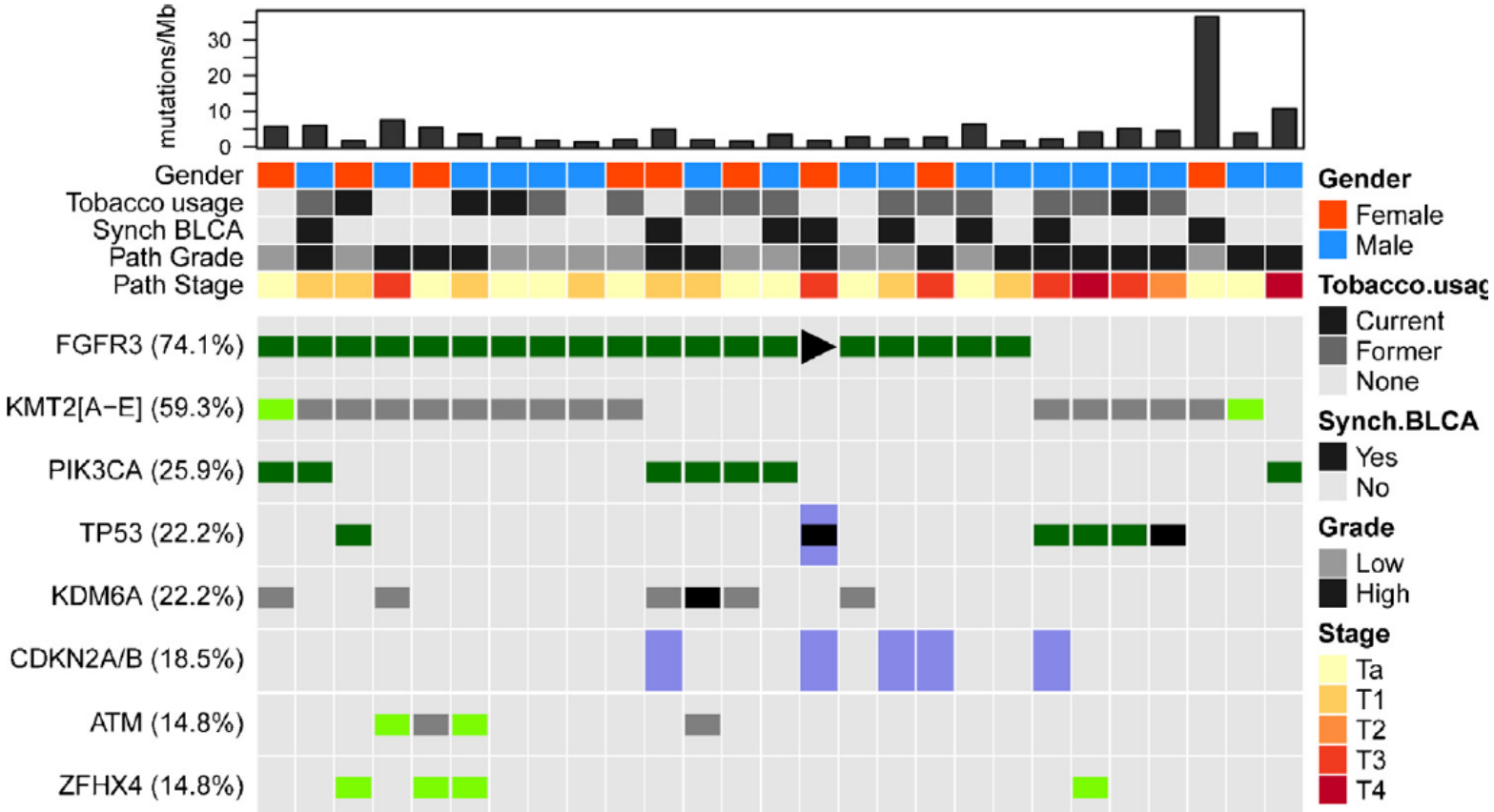
Aurélie Mbeutcha[1,2] · Morgan Rouprêt[3] · Ashish M. Kamat[4] · Pierre I. Karakiewicz[5] · Nathan Lawrentschuk[6] · Giacomo Novara[7] · Jay D. Raman[8] · Christian Seitz[1] · Evanguelos Xylinas[9] · Shahrokh F. Shariat[1,10,11]

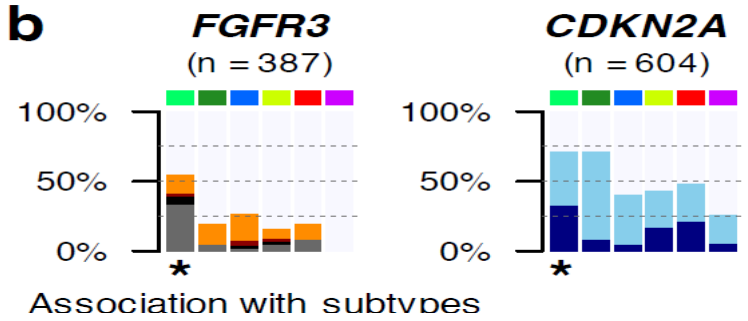
Results A total of 116 studies were included in this review. These large and/or multi-institutional studies have confirmed the prognostic value of standard pathological factors (i.e., tumor stage, grade and lymph node metastasis) and identified novel features such as lymphovascular invasion, tumor architecture, multifocality, concomitant CIS, variant histology and biomarker status among others. Based on these variables, several predictive tools have been developed; however, they often lack of validation. The value of these features and tools needs prospective testing.

2016 WJU

Comprehensive Genomic Characterization of Upper Tract Urothelial Carcinoma

Tyler J. Moss [a], Yuan Qi [a], Liu Xi [b], Bo Peng [a], Tae-Beom Kim [a], Nader E. Ezzedine [d], Maribel E. Mosqueda [d], Charles C. Guo [e], Bogdan A. Czerniak [e], Michael Ittmann [f], David A. Wheeler [c], Seth P. Lerner [g,], Surena F. Matin [h,**]*

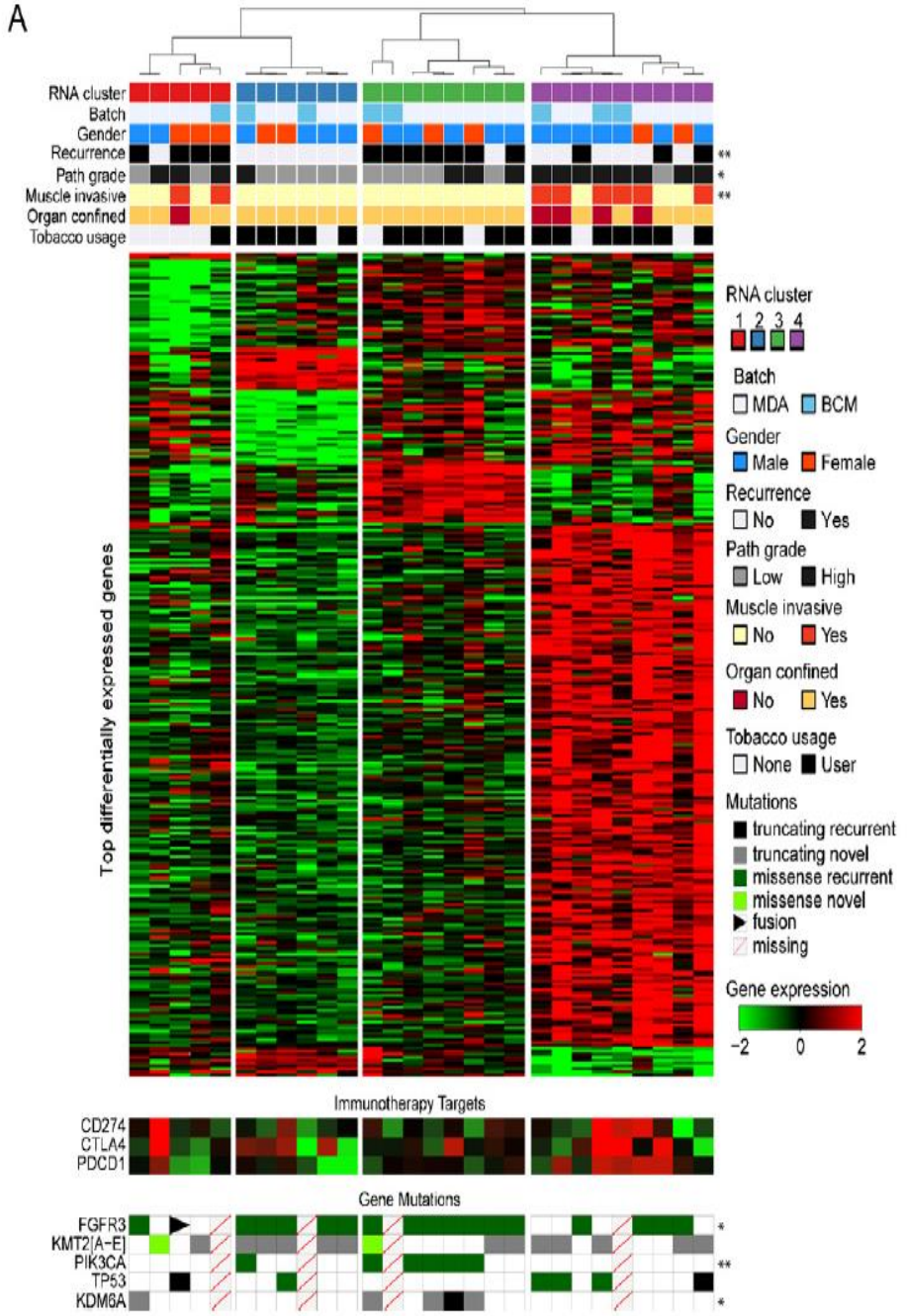




Eur Urol 2015, Kamoun Eur Urol 2020

Genetics

- RNA-clusters
- Comparison with TCGA
- Clusters→ basal-like
- Clusters close to luminal
- Each sub-type
  - Molecular specificity
  - 4 different clusters



Cluster 2

100% FGFR3 mutations
LG
Tobaccho
Non-invasive
No recurrence

Cluster 3

100% FGFR3 mut, 71% PIK3CA mut, no TP53 mut
Tobaccho
All tumors <pT2
Recurrence

Cluster 1

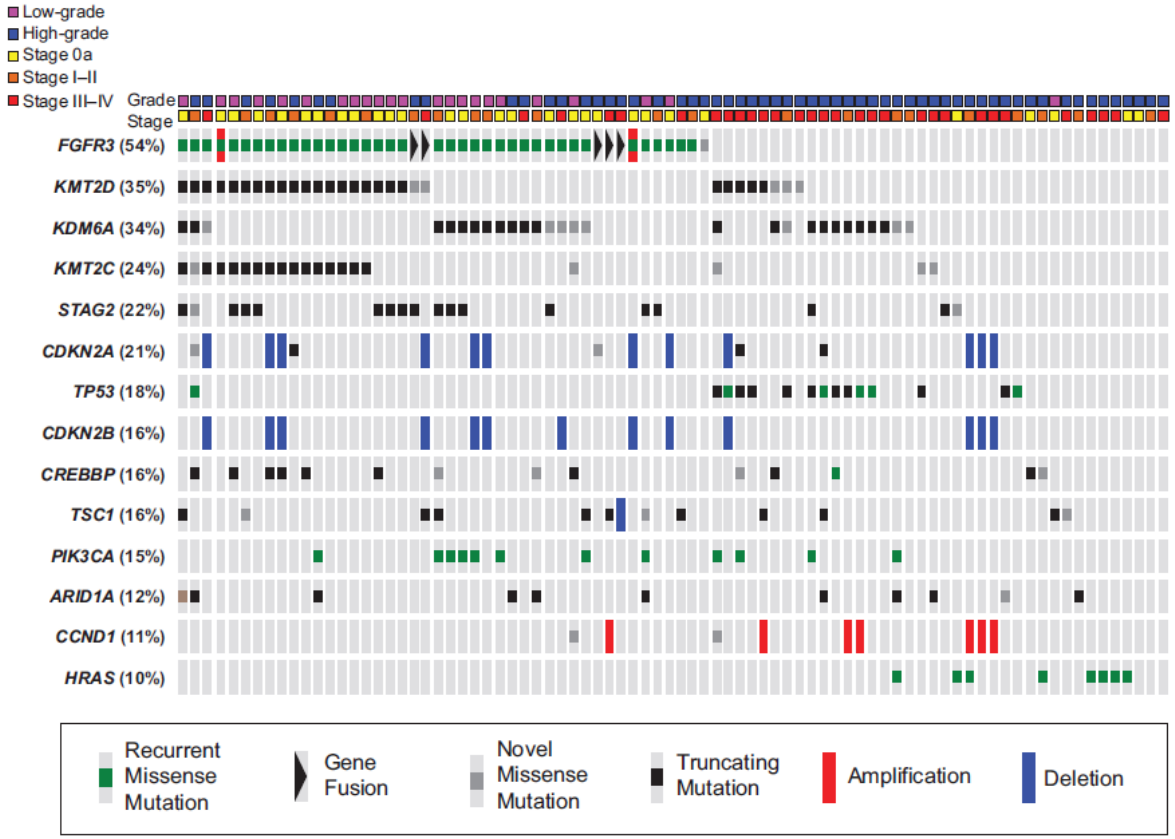
NO PIK3CA mutations
Non-smoker
HG <pT2
High recurrence

Cluster 4

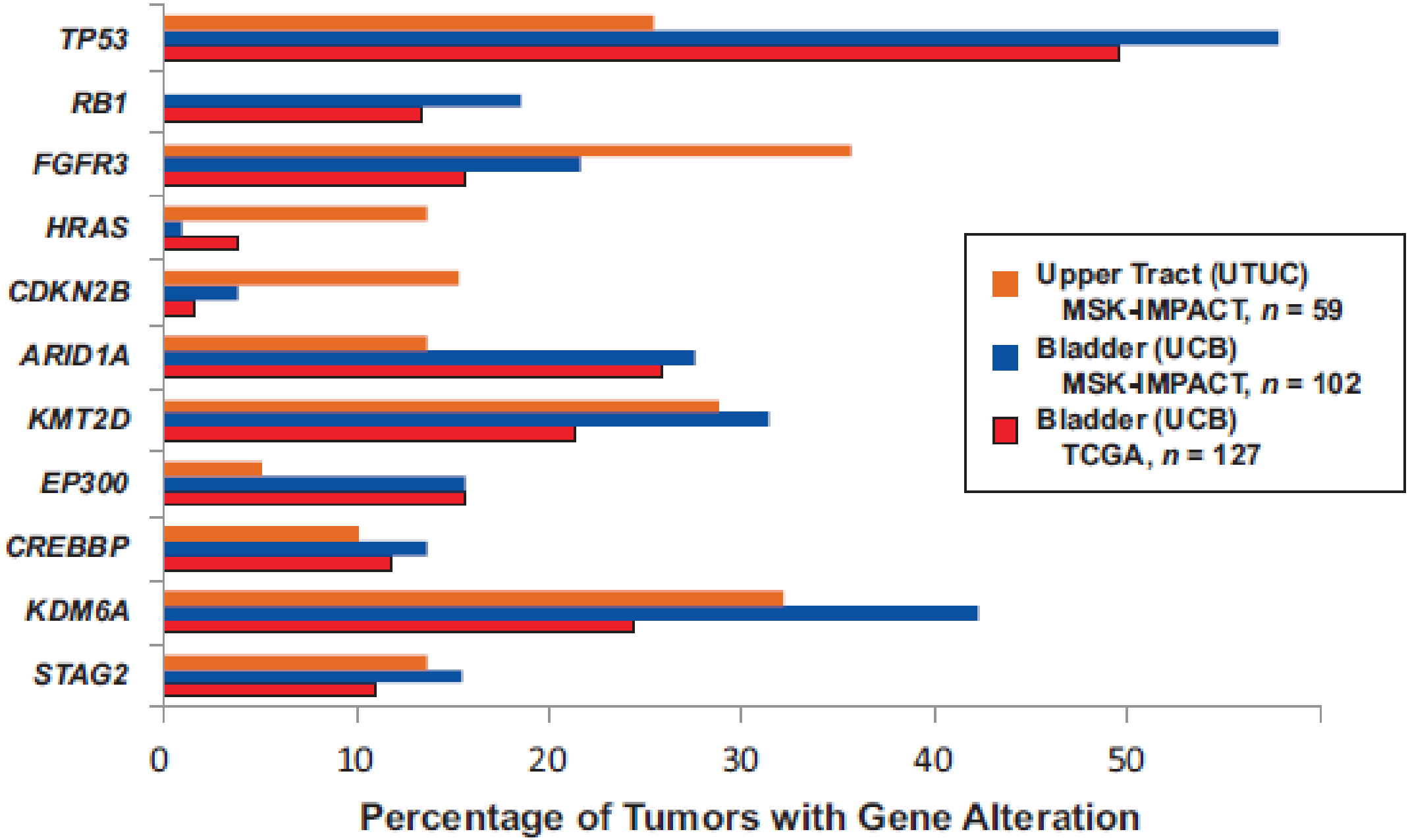
50% FGFR3 mut, 50% TP53 mut, no PIK3CA mut
HG ≥ pT2, Cis
Tobaccho
Short survival

Comparison UTUC and UBCa

- HG UTUC and UBCa
  - Significant differences in prevalence of somatic alterations
- HG UTUC *vs* UBCa
  - *FGFR3* (36 *vs* 21%)
  - *HRAS (*14 *vs* 1%)
  - CDKN2B (15 *vs* 4%)
  - Less mutated
    - *TP53* (25-58%)
    - *RB1* (0-18%)
    - *ARIDA1A* (13-27%)
- UTUC many targetable alterations



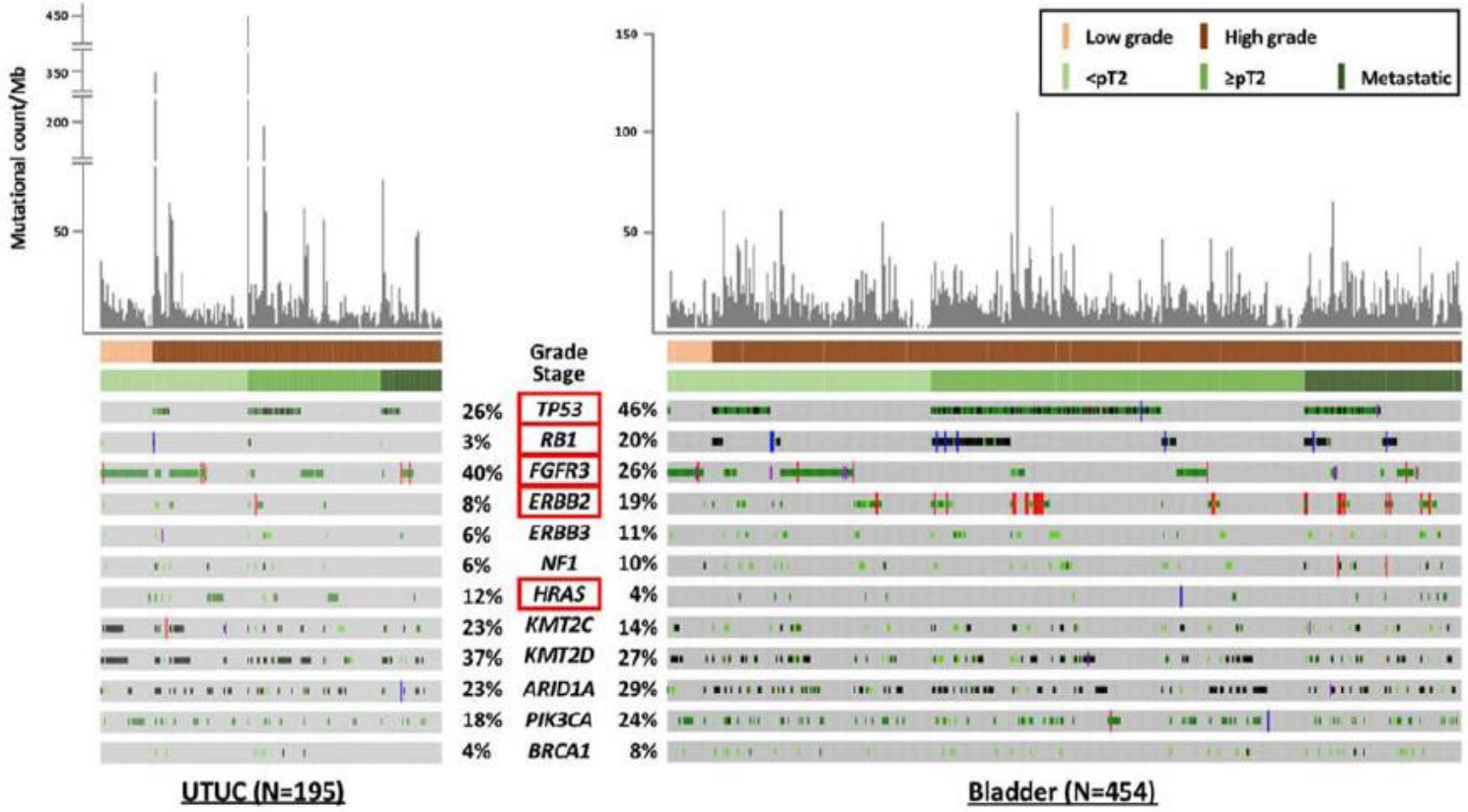
Sfakianos Eur Urol 2016

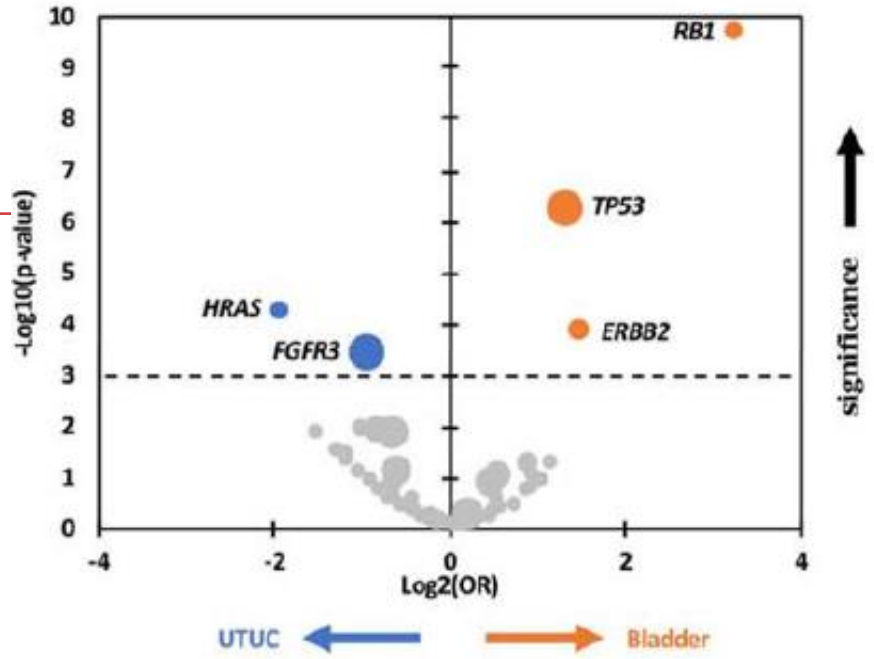


Sfakianios, Eur Urol 2015

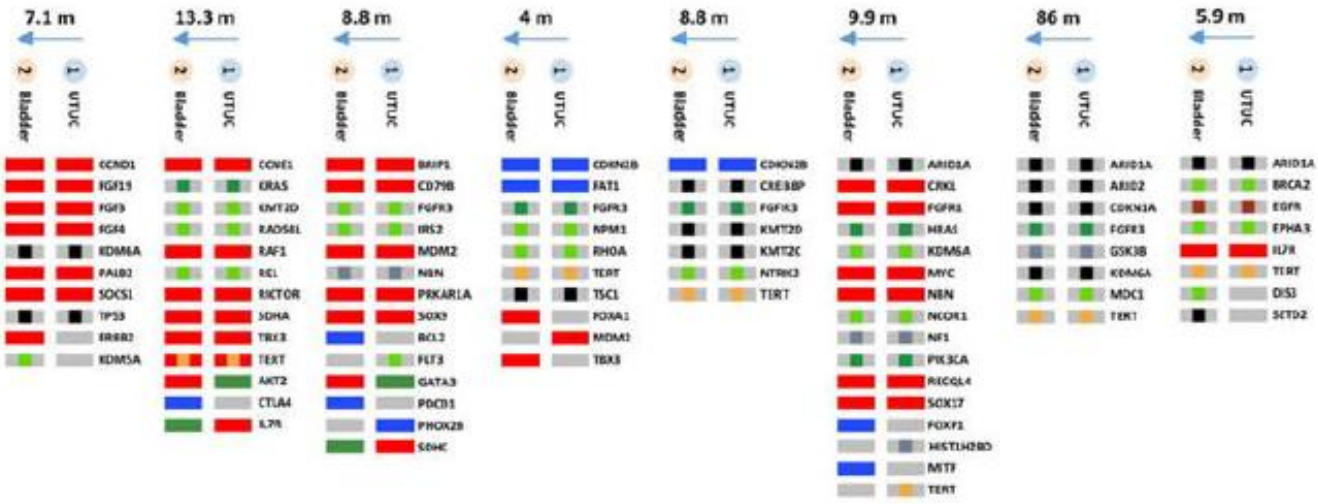
Clonal relatedness and mutational differences between upper tract and bladder urothelial carcinoma

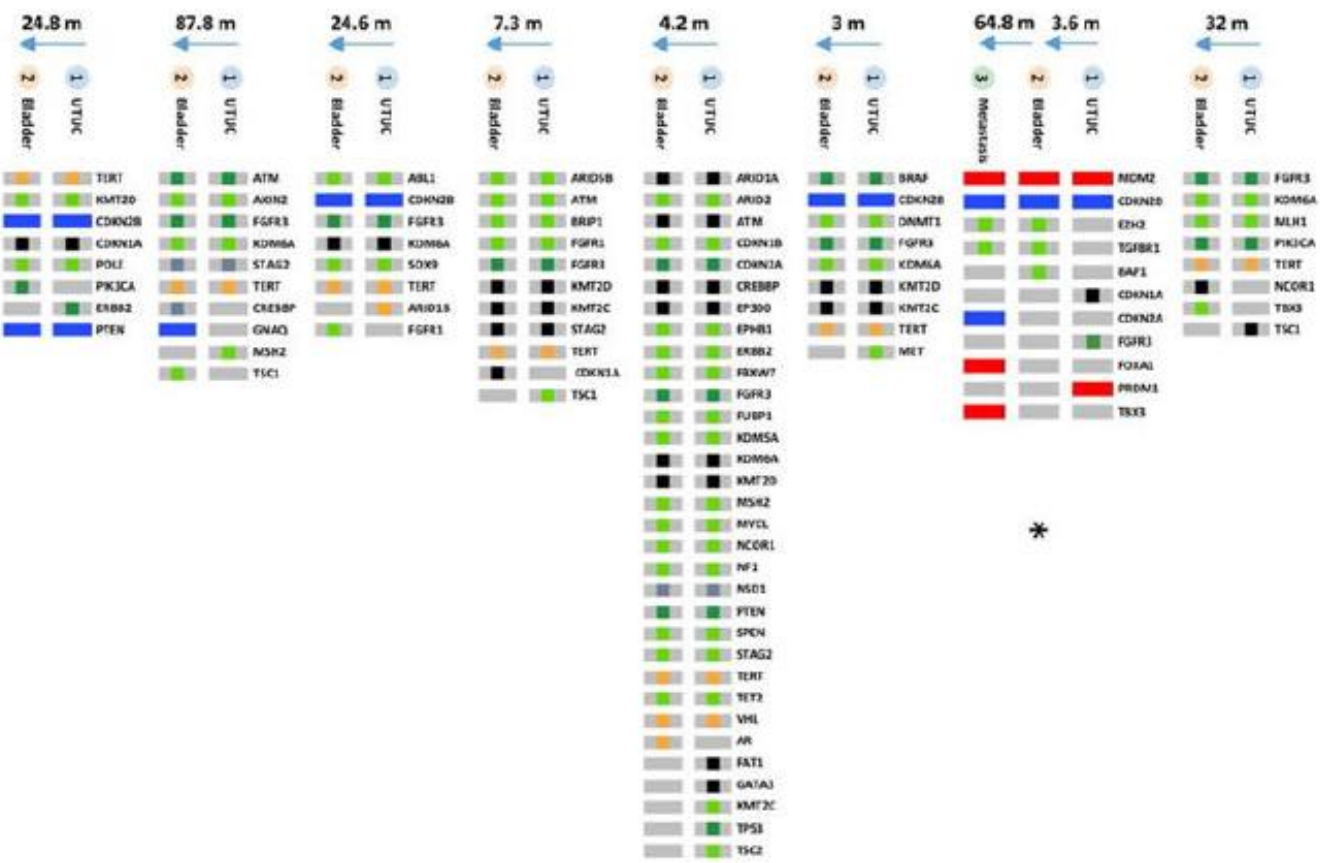
François AUDENET[#1], Sumit ISHARWAL[#1], Eugene K. CHA[1], Mark T. A. DONOGHUE[2,3], Esther N. DRILL[2], Irina OSTROVNAYA[2], Eugene J. PIETZAK[1], John P. SFAKIANOS[4], Aditya BAGRODIA[5], Paari MURUGAN[6], Guido DALBAGNI[1], Timothy F. DONAHUE[1], Jonathan E. ROSENBERG[7], Dean F. BAJORIN[7], Maria E. ARCILA[3,8], Jaclyn F. HECHTMAN[8], Michael F. BERGER[3,8], Barry S. TAYLOR[2,3], Hikmat AL-AHMADIE[3,8], Gopa IYER[3,7,9], Bernard H. BOCHNER[1,9], Jonathan A. COLEMAN[1,*], and David B. SOLIT[3,7,9,*]

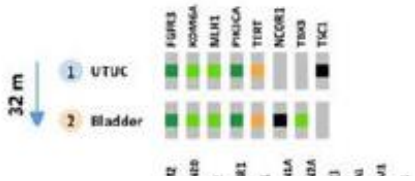


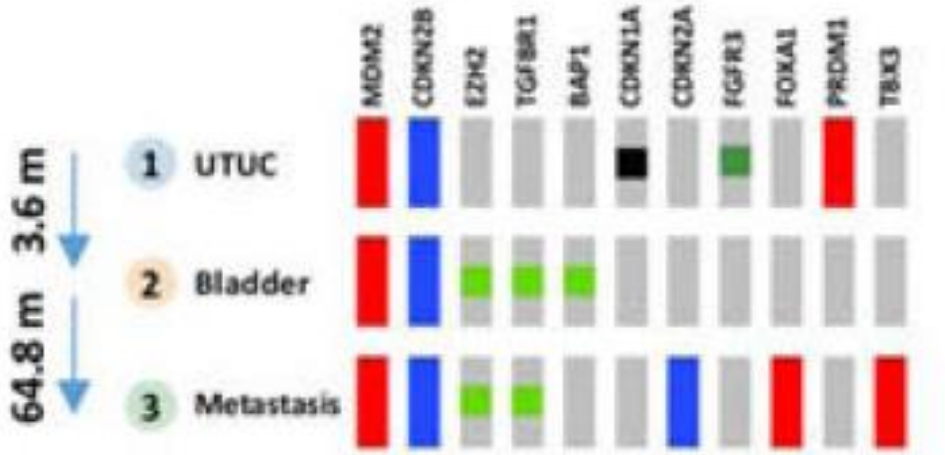


Risk of bladder recurrence if
FGFR3, KDM6A, CCND1, TP53 mutations
If both tumors clonally related


7.1 m
13.3 m
8.8 m
4 m
8.8 m
9.9 m
86 m
5.9 m
2 Bladder
1 UTUC
CCND1
FGF19
FGF3
FGF4
KDM6A
PAIK2
SOCS1
TP53
ERBB2
KDM5A
CCNE1
ERAS
KMT2D
RAD50L
RAF1
RICL
RICTOR
SDHA
TBX3
TERT
AKT2
CTLA4
IL7R
BRIP1
CD79B
FGFR3
IRS2
MDM2
NBN
PRKAR1A
SOX9
BCL2
FLT3
GATA3
PDCD1
PHOX2B
SDHC
CDKN2B
FAT1
FGFR3
NPM1
RHOA
TERT
TSC1
FOXA1
MDM2
TBX3
CDKN2B
CREBBP
FGFR3
KMT2D
KMT2C
NTRK3
TERT
ARID1A
CRK1
FGFR1
HRAS
KDM6A
MYC
NBN
NCOR1
NF1
PIK3CA
RECQL4
SOX17
FOXF1
HIST1H2BD
MET
TERT
ARID1A
ARID2
CDKN1A
FGFR3
GSK3B
KDM6A
MDC1
TERT
ARID1A
BRCA2
EGFR
EPHA3
IL7R
TERT
DIS3
SCTD2

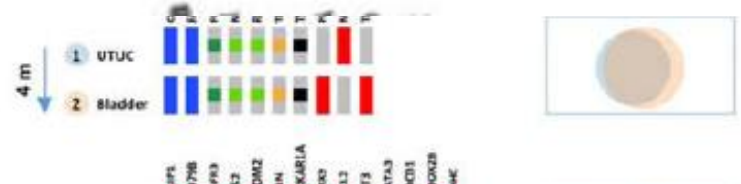

24.8 m
87.8 m
24.6 m
7.3 m
4.2 m
3 m
64.8 m
3.6 m
32 m
2 Bladder
1 UTUC
3 Metastasis
TERT
KMT2D
CDKN2B
CDKN1A
POLE
PIK3CA
ERBB2
PTEN
ATM
AXIN2
FGFR3
KDM6A
STAG2
TERT
CREBBP
GNAQ
NSD2
TSC1
ABL1
CDKN2B
FGFR3
KDM6A
SOX9
TERT
ARID1B
FGFR1
ARID1B
ATM
BRIP1
FGFR1
FGFR3
KMT2D
KMT2C
STAG2
TERT
CDKN1A
TSC1
ARID1A
ARID2
ATM
CDKN1B
CDKN2A
CREBBP
EP300
EPHB1
ERBB2
FBXW7
FGFR3
FUBP1
KDM5A
KDM6A
KMT2D
MSH2
MYCL
NCOR1
NF1
NSD1
PTEN
SPEN
STAG2
TERT
TET2
VHL
AR
FAT1
GATA3
KMT2C
TP53
TSC2
BRAF
CDKN2B
DNMT3
FGFR3
KDM6A
KMT2D
KMT2C
TERT
MET
MDM2
CDKN2B
EZH2
TGFBR1
BAP1
CDKN1A
CDKN2A
FGFR3
FOXA1
PRDM1
TBX3
FGFR3
KDM6A
MLH1
PIK3CA
TERT
NCOR1
TBX3
TSC1

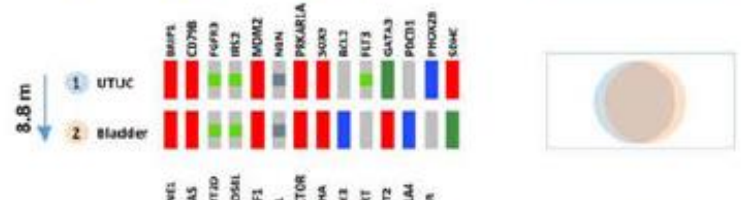


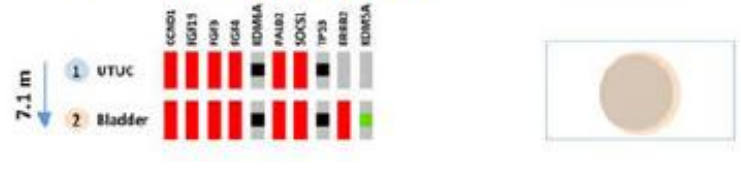


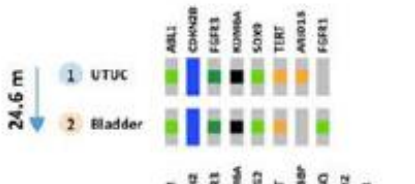
*

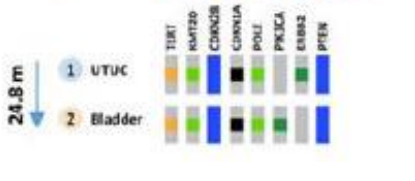
Metastases closer to UC than UTUC









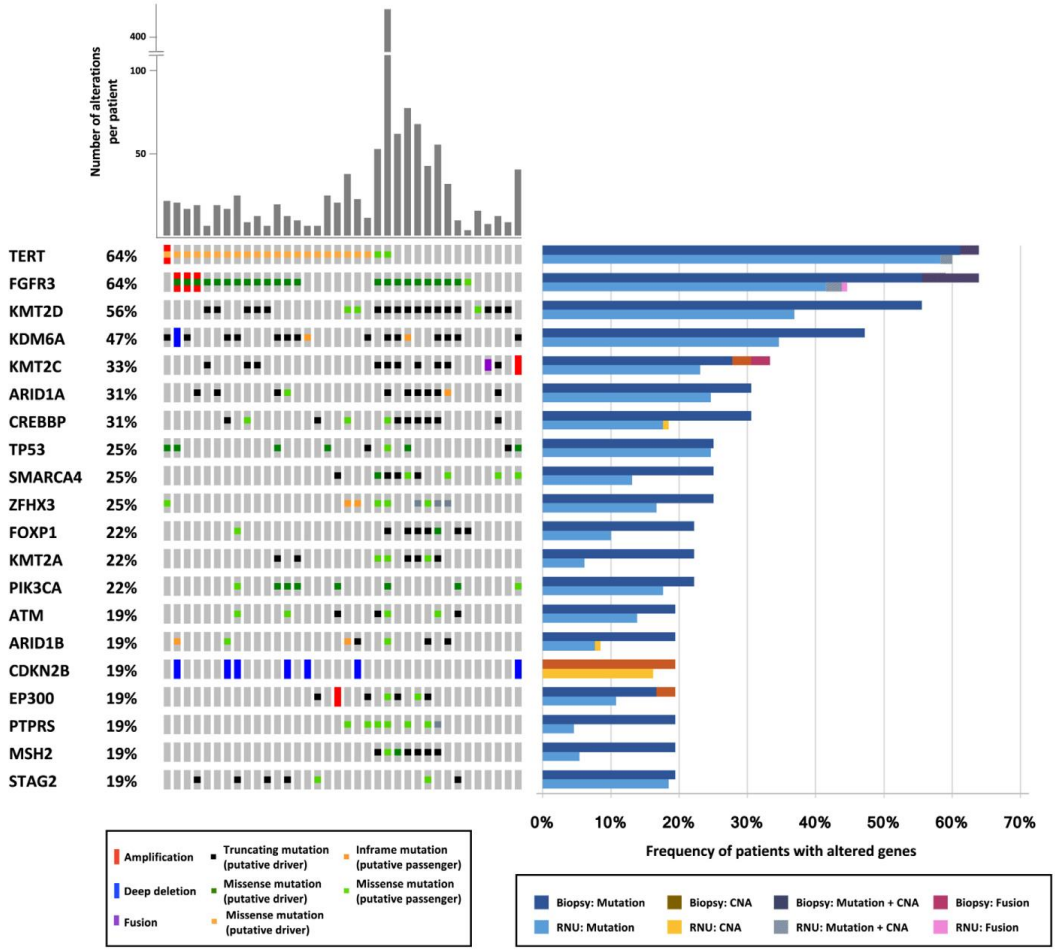


Genomic Profile of Urothelial Carcinoma of the Upper Tract from Ureteroscopic Biopsy: Feasibility and Validation Using Matched Radical Nephroureterectomy Specimens

Aditya Bagrodia [a,†], Francois Audenet [b,†], Eugene J. Pietzak [b], Kwanghee Kim [b], Katie S. Murray [b], Eugene K. Cha [b], John P. Sfakianos [c], Gopa Iyer [d], Nirmish Singla [a], Maria Arcila [e], Bernard H. Bochner [b], Hikmat A. Al-Ahmadie [e], David B. Solit [d], Jonathan A. Coleman [b,]*

- 92% of biopsies material sufficient
- *TERT* promoter 64%
- *FGFR3* 64%

- Molecular characterization biopsies
  - Guide treatment
  - Helps in decision making
  - Identify high risk patients
    - NAC
    - Organ-sparing



Lynch syndrome (LS)

- Autosomal dominant
- Germcell mutations of DNA MMR genes
- Amsterdam 1&2 criteria, Bethesda guidelines
- UTUC treatment varies whether sproadic or LS
  - Rare → 2 new cases /100000
- Link with pathologist & genetic oncologist++ (IHC, RT-PCR)

Upper Urinary Tract Urothelial Carcinoma in Lynch Syndrome Patients: The Urologist Still Has a Role in Genetic Screening

Elisabeth Grobet-Jeandin[a,b], *Ugo Pinar*[a], *Morgan Rouprêt*[a,*]

Immunohistochemical Screening of Upper Tract Urothelial Carcinomas for Lynch Syndrome Diagnostics: A Systematic Review

Maria Rasmussen, Mia Gebauer Madsen, and Christina Therkildsen

- Universal staining for MMR loss
- LS in 4.7%
- Ureter more often

- Mostly loss of hMSH2 and hMSH6
  - Heterogeneity of hMSH6 expression
  - Testing less efficient than in colorectal cancers?
  - All immediately RT-PCR?
- MSI-High instability of 2 ore more marker

Urology 2022, Clinical Genitourinary Cancer 2020

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Loss of Mismatch-repair Protein Expression and Microsatellite Instability in Upper Tract Urothelial Carcinoma and Clinicopathologic Implications

Björn Schneider,[1] Änne Glass,[2] Sandra Jagdmann,[3] Maja Hühns,[1] Jessica Claus,[1] Heike Zettl,[4] Desiree-Louise Dräger,[5] Matthias Maruschke,[5,6] Oliver W. Hakenberg,[5,6] Andreas Erbersdobler,[1] Annette Zimpfer[1]

chemotherapy. **Conclusion:** The frequency of MSI in UTUC was 36 (28.1%) of 128 patients with a good accuracy of immunohistochemistry. In daily practice, MSI screening especially is recommended in patients with advanced UTUC

- Mostly loss of hMSH2 and hMSH6
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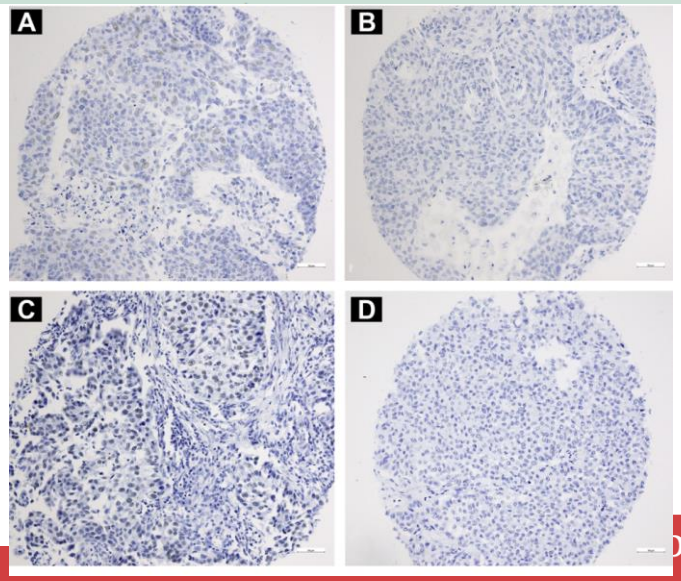


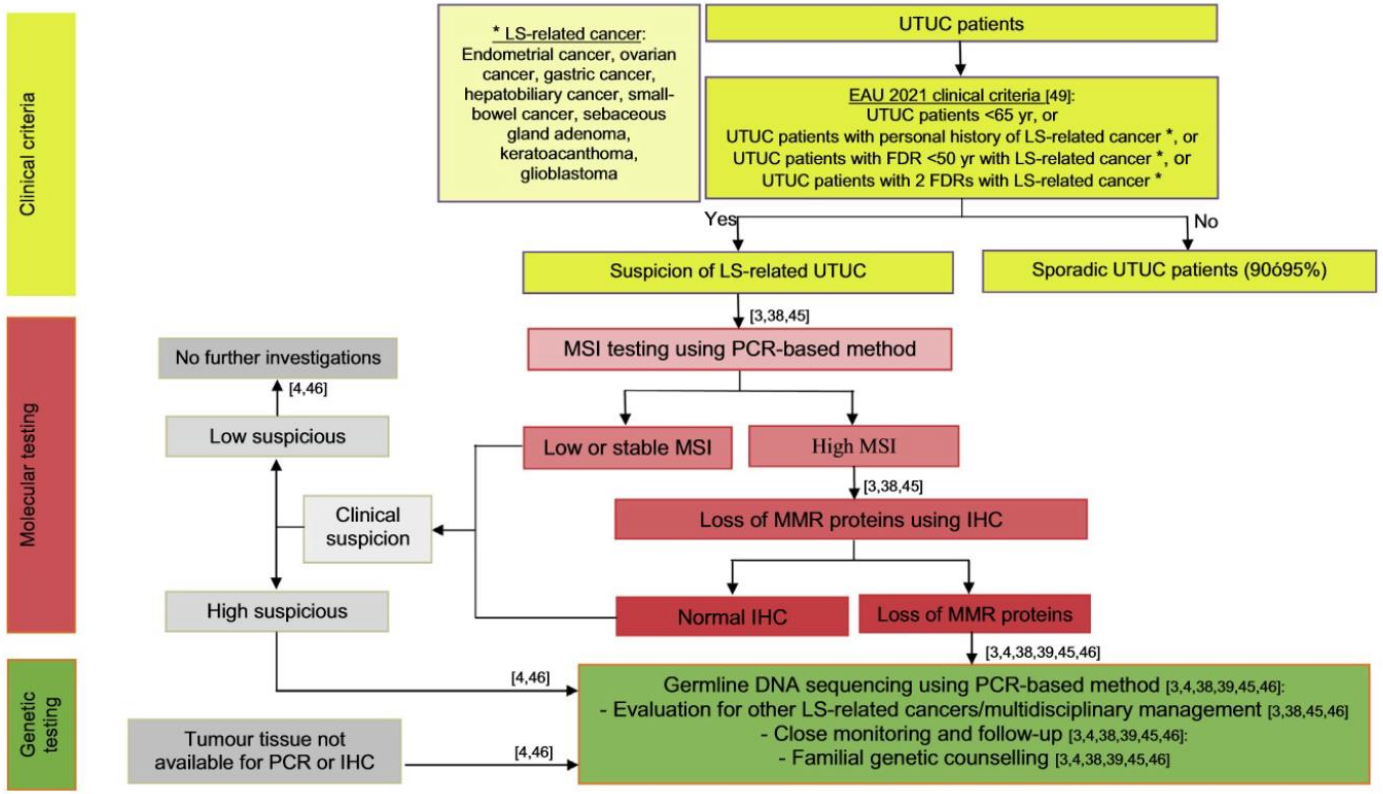
Urology 2022, Clinical Genitourinary Cancer 2020

Upper Tract Urothelial Carcinoma in the Lynch Syndrome Tumour Spectrum: A Comprehensive Overview from the European Association of Urology - Young Academic Urologists and the Global Society of Rare Genitourinary Tumors

Chiara Lonati [a,b,], Andrea Necchi [c,d], Juan Gómez Rivas [e], Luca Afferi [b], Ekaterina Laukhtina [f,g], Alberto Martini [h], Eugenio Ventimiglia [h], Renzo Colombo [h], Giorgio Gandaglia [h], Andrea Salonia [c,h], Alberto Briganti [c,h], Francesco Montorsi [c,h], Agostino Mattei [b], Claudio Simeone [a], Maria I. Carlo [i], Shahrokh F. Shariat [f,g,j,k,l], Philippe E. Spiess [m], Marco Moschini [b,h], on behalf on the European Association of Urology Young Academic Urologists EAU-YAU: Urothelial Carcinoma Working Group, the Global Society of Rare Genitourinary Tumors GSRGT*

- UTUC 3rd most common

  Lynch syndrome (LS) related tumor
  - 14x risk of UTUC
  - 75x if hMSH2
  - Younger (p=0.005) F>M
  - Ureteral location (p=0.01)
- No consensus on screeing protocols
- Urinary cytology not recommended
  - Sensitivity 29%



Eur Urol 2022

Current Advances in Immune Checkpoint Inhibition and Clinical Genomics in Upper Tract Urothelial Carcinoma: State of the Art

Gianluigi Califano [1,2], Idir Ouzaid [2], Paul Laine-Caroff [2], Arthur Peyrottes [2], Claudia Collà Ruv Benjamin Pradère [3], Vincent Elalouf [4], Vincent Misrai [5], Jean-François Hermieu [2], Shahrokh F. S and Evanguelos Xylinas [2,6,*]

primary tumor location. Actually, sporadic UTUC has a luminal–papillary T-cell-depleted contexture and activated FGFR3 signaling. In addition, upregulation of FGFR3 in UTUC seems to be associated with a lower CD8 T-cell gene signature and, more interestingly, it has been shown to be important in shaping the observed T-cell-depleted phenotype [38]. Consequently, sporadic UTUC should frequently be characterized by an immune desert profile and refractoriness to immunotherapy. In contrast, UTUC developed in a Lynch syndrome context exhibits high MSI and TMB. According to these biological features, it could be considered an immune hot tumor. However, the profiles depicted did not match the clinical outcomes reported in the leading studies investigating the efficacy of immunotherapy in UTUC [7]. Again, this is indirect evidence that a significant knowledge

Therkildsen, Clin and Experimental Gastroenterology 2021

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REVIEW

An Update on Immune Checkpoint Therapy for the Treatment of Lynch Syndrome

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Efficacy of Immune Checkpoint Inhibitors in Upper Tract Urothelial Carcinomas: Current Knowledge and Future Directions

Jonathan Thouvenin [1,2,*], Nieves Martínez Chanzá [2], Omar Alhalabi [3], Hervé Lang [4], Nizar M. Tannir [3], Philippe Barthélémy [1] and Gabriel G. Malouf [1,*]

ICI inhibitors are now widely used in daily practice to treat urothelial carcinoma patients. Based on the recent advancement in the comprehension of the molecular biology of UTUC and the differences between bladder UC and UTUC, further studies focused on UTUC patients are needed to personalize the therapeutic approach and find new treatment combinations.

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Screening

- Which population?
- All known LS patients
- No consensus about screening
- Only hMSH2 mutation carriers?
- Patients with a family history of BC
- Starting at age …? (25-50y suggested)
- Urinary cytology
- Urinanalysis
- Abdominal ultrasound-CT

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→ If newly diagnosed multidisciplinary management

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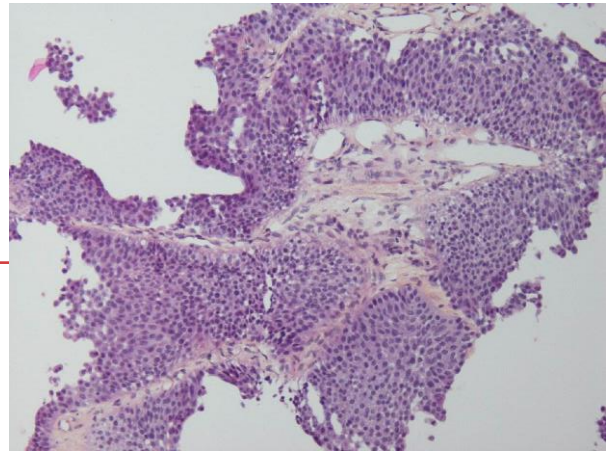
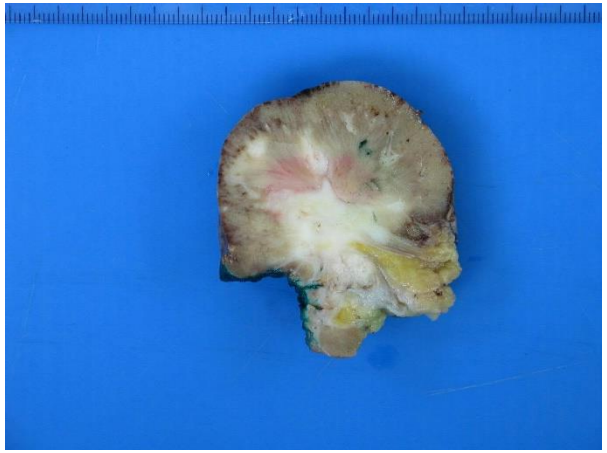
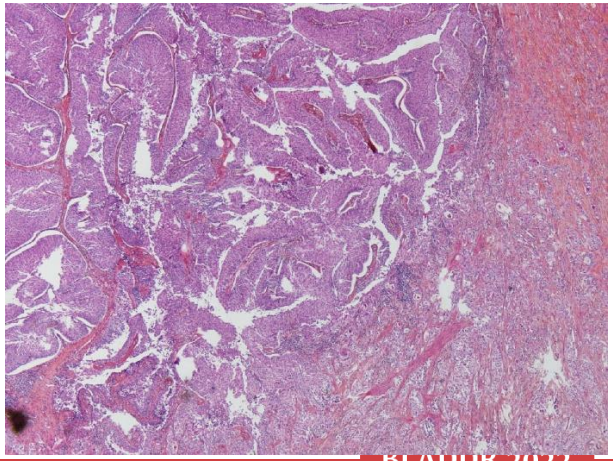
Take home

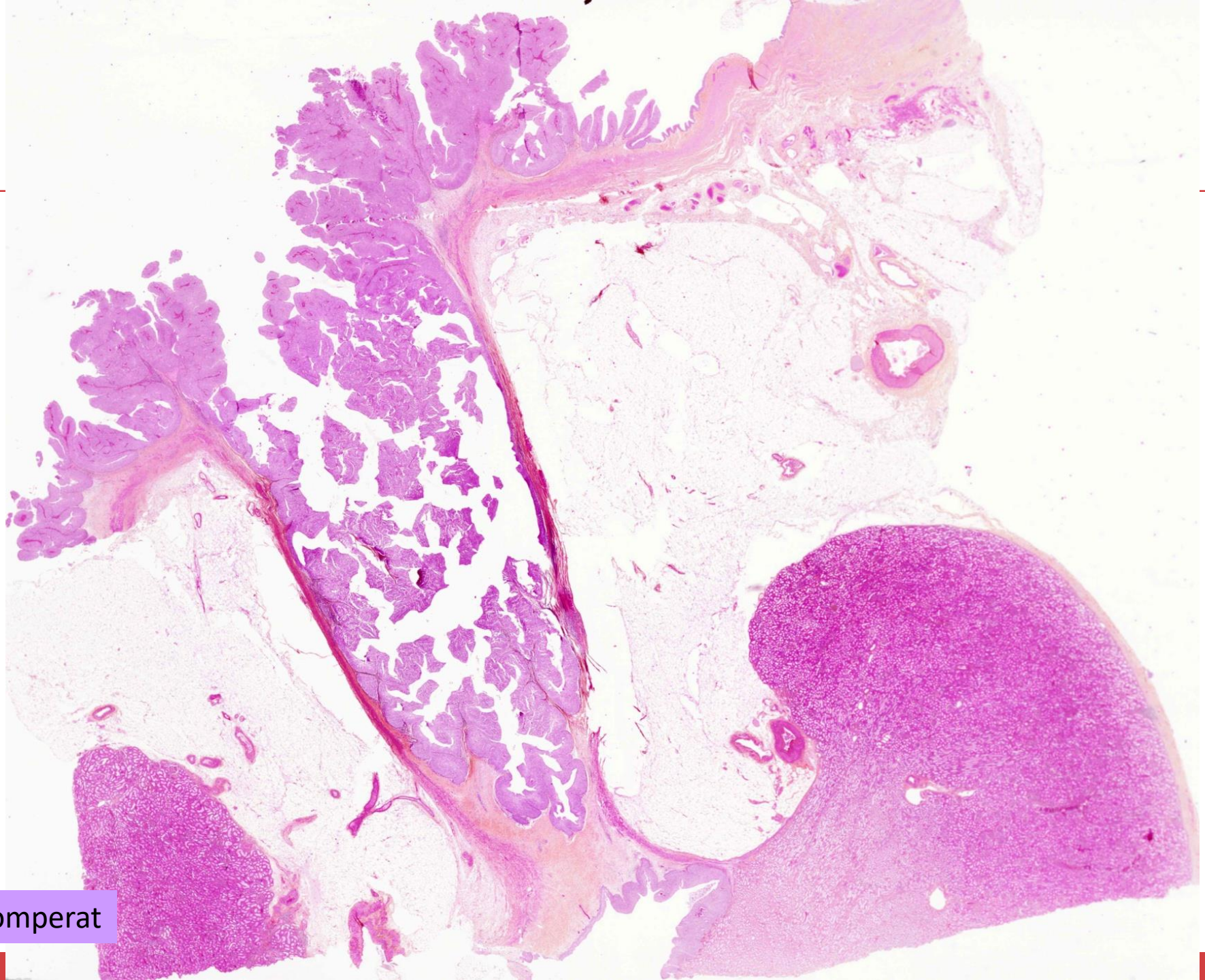
- Histology → same, but caution!!
  - Tumor heterogeneity
  - Same factors of risk
- Different genetic alterations in bladder und UUT
  - *TP53/FGFR3*
- Bladder and UTUC
  - Different molecular groups predominant
  - UTUC test MSI+++

- If both tumors present
  - Clonal relationship
- Disparate twins….









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