Understanding Upper Tract UC Biology

BAUS Section of Oncology
Belfast 2012

Mr David R Yates

Consultant Urological Surgeon

Royal Hallamshire Hospital

Sheffield

Upper Tract UC vs. Bladder UC

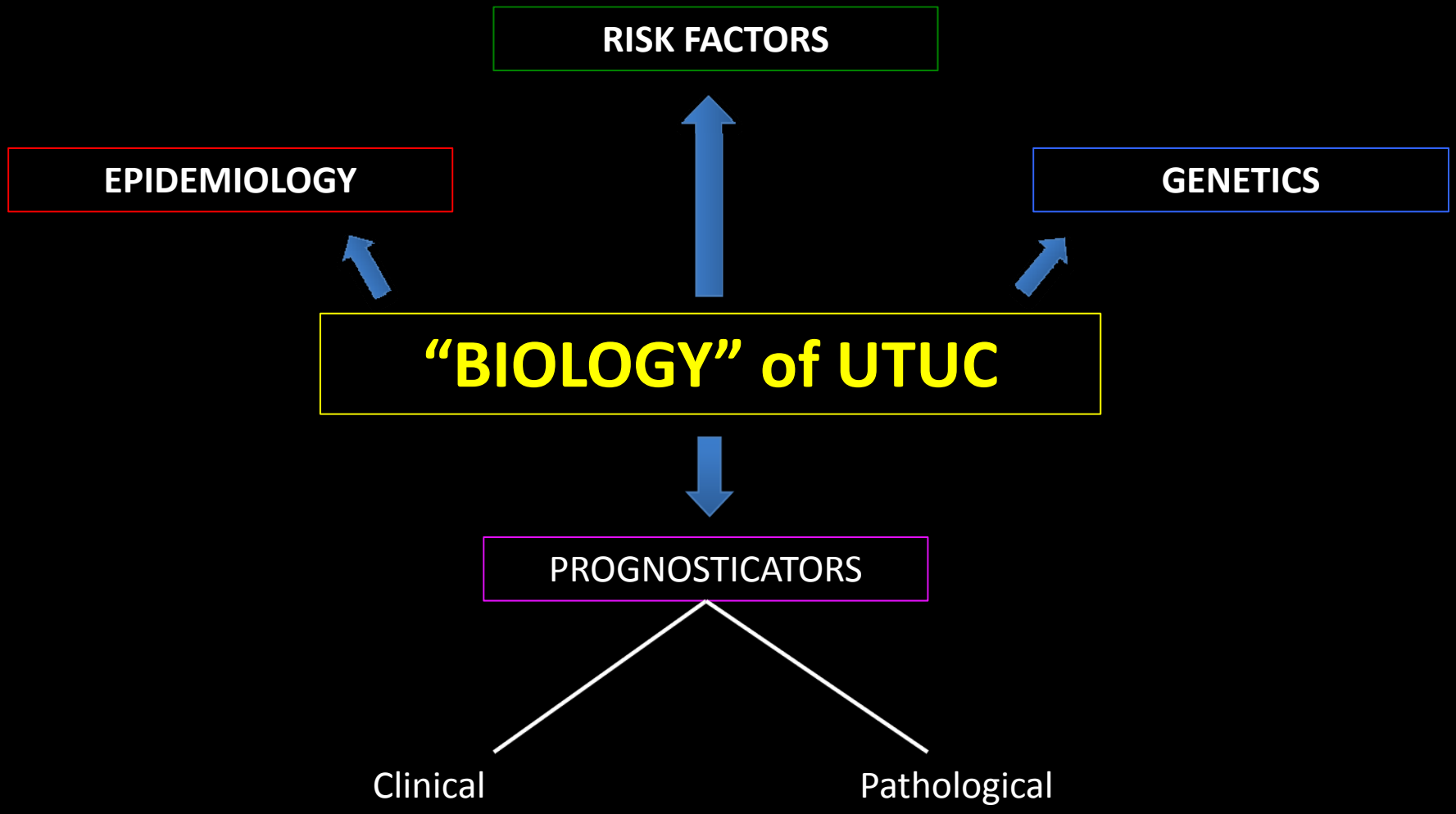
Same or Different?

STRUCTURAL and FUNCTIONAL DIFFERENCES:

1. Storage vs. Excretion
2. Increased exposure time to carcinogens in bladder
3. Increased number of urothelial cells in bladder
4. Increased thickness of m.propria in bladder

"It is now obvious that epidemiological and genetic data exist to suggest that strong differences exist between the lower and upper urinary tract"

Lughezzani et al. Eur Urol 2012;62:100-114


RISK FACTORS
EPIDEMIOLOGY
GENETICS
"BIOLOGY" of UTUC
PROGNOSTICATORS
Clinical
Pathological

Basics of UTUC vs. Bladder

- **For UTUC, patients are:**
  1. **Older**: peak 75 (vs. 65 bladder)

- **For UTUC, tumours are:**
  1. **Rarer**: Europe 2/100,000 vs.14-24/100,000
  2. **More invasive** at diagnosis: 60% ≥pT1 (vs. 15-30% bladder)
  3. **Higher grade** at diagnosis: 70-85% ≥G2
  4. **Part of a familial cancer syndrome**: HNPCC

Matsumoto et al. BJU Int 2011;108:304-9
Raman et al. BJU Int 2011;107:1059-64
Hall et al. Urology 1998;52:594-601
Stewart et al. BJU Int 2005;95:791

SOME UTUC STATISTICS

- Account for **5%** UCs overall
- Account for **10%** of 'renal' tumours
- Concurrent Bladder UC = **8-13%**

1. **MULTIFOCALITY**
2. **URINE FLOW**

- Previous Nephroureterectomy

  Metachronous UTUC = **2-6%**

  Metachronous bladder tumour = **30-50%**

- Previous Bladder UC

  Metachronous UTUC in **0.5-2%** but if reflux then **6-20%**

Raman et al. BJU Int 2011; 107:1059-64, Amar et al. J Urol 1985; 133; 468-471, Roupret et al. Eur Urol 2011; 59:584-594

Risk factors generic to UC

- **SMOKING**

  x3.1 RR McLaughlin et al. Cancer Res 1992; 52: 254-7

  x7.2 RR if >45-yrs smoker (e.g dose related)

- **OCCUPATION**

  x8.3 RR Colin et al. BJU Int 2009; 104: 1436-40

  same agents as bladder (e.g aromatic amines)

Specific risk factors to UTUC

- **Aristocholic Acid Induced Nephropathies**
  - **1. "Chinese Herb" nephropathy**
  - **2. "Balkans Endemic" nephropathy**

- AA compounds found in ***Aristolochia*** plant species of which there are 500 species

- Both nephropathies thought to be related with AA compounds causing interstitial nephritis, progression to ESRD and increase risk of urothelial cell malignancy

Chinese Herb Nephropathy

- *Aristolochia* plants commonly used in Chinese herbal medicine
- ***Aristolochia. Fangchi*** *in* Mu Fang Ji herbal medication ('weight reduction' treatment)
- 90% of UCs are in renal pelvis

Nortier et al. NEJM 2000;342:1686-92

Balkans Endemic Nephropathy

- ***Aristocholic. Clematis***
- Accidentally ingested due to contaminated flour supply around tributaries of **Danube River**

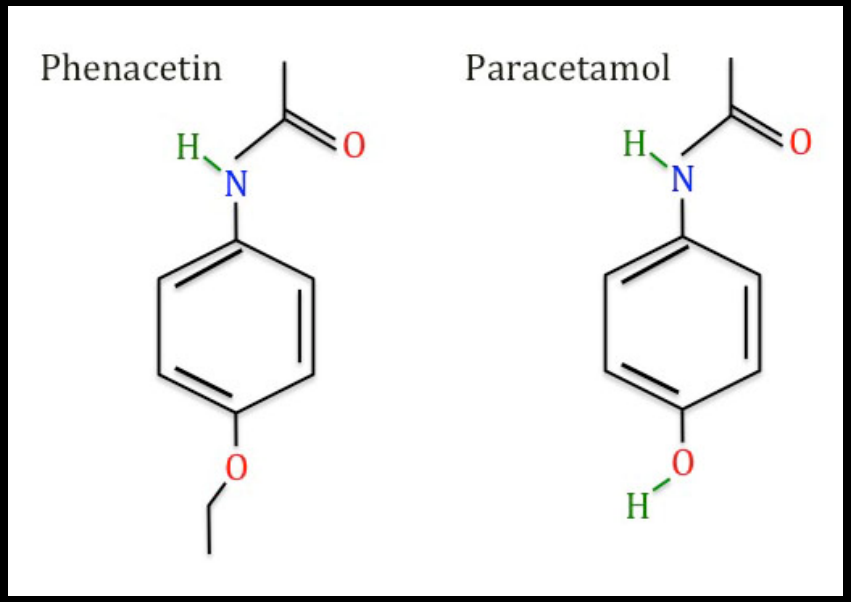
- **x100 RR UTUC** Grollman et al. PNAS 2007;104:12129

Specific risk factors to UTUC

Phenacetin Analgesics

- Introduced in 1887
- **RR 5.4-12.2** vs. 2.6 bladder McCredie et al. Int J Cancer 1993;53:245-249
- Removed from market in 1983
- Metabolised to Paracetamol

Phenacetin Structure



Can you imagine if Paracetamol had same carcinogenic effect?
30 million ‘packs’ sold each year in UK!
No other true rival to Paracetamol

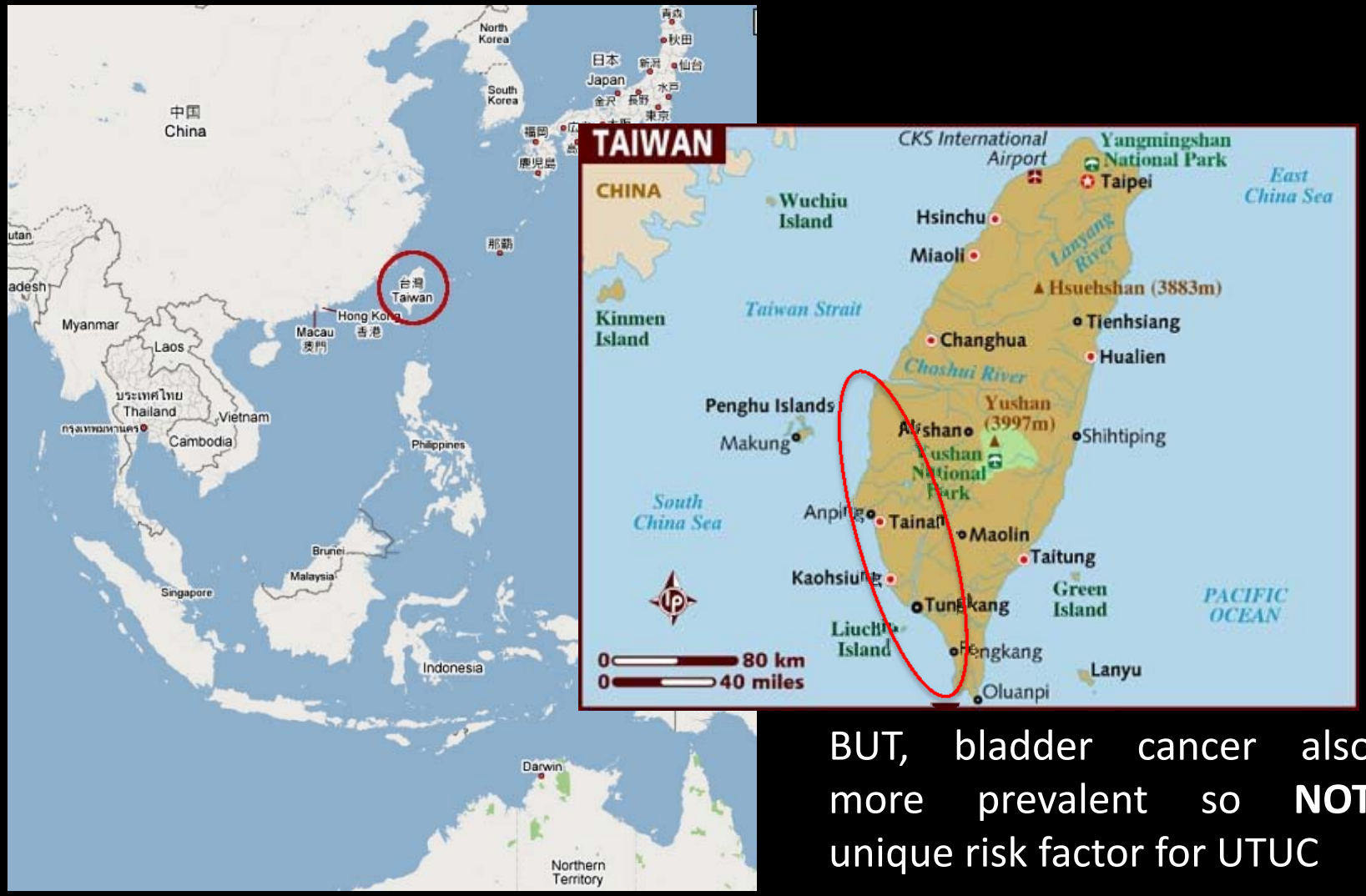
Specific risk factors to UTUC

Blackfoot Disease

- Unique peripheral vascular disease common to Taiwan
- Increased risk cancer: skin, lung, liver and **urinary tract**
- Due to high **arsenic** levels in water

Tan et al. BJU Int 2008;102:48-54

South West territory ‘endemic’ area



BUT, bladder cancer also more prevalent so **NOT** unique risk factor for UTUC

GENETICS of UTUC

- Molecular biology of UTUC and bladder thought to be largely similar e.g Chr.9, FGFR3, p53, pRb
- UC is a “pan-urothelial” entity
- Gene Expression profiling reveals few differences
  Zhang et al. BMC Med Genomics 2012; 3:58
- Clonality studies suggest tumours related
  Catto et al. J Urol 2006;175:2323
- But there are distinct genetic differences:

  1. Microsatellite Instability (MSI)

  2. DNA Hypermethylation

Microsatellite Instability

- **Q: What is a microsatellite?**
- A: Short tandem repeat sequences of DNA (e.g CC, GGG, TTTT, AAAAA) scattered throughout genome

- **Q: What is instability?**
- A: Single base point mutations (insertion or deletion of nucleotides) that leads to a reading frameshift that can be detrimental if within coding regions of key target genes

- **Q: Why does it happen?**
- A: Inactivation of DNA mismatch repair system

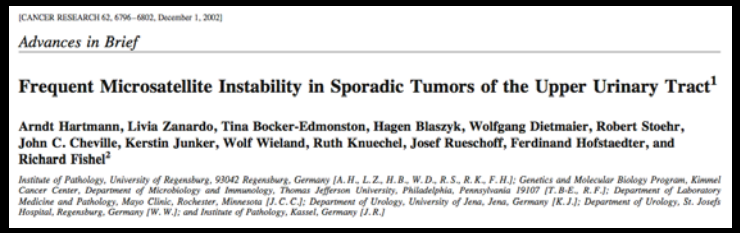
Catto et al. Oncogene 2003; 22:8699-8706

MSI in UTUC

- **Frequency of MSI in UTUC = 13-21%**
  Hartmann et al. Cancer Res 2002; 62: 6796; Catto et al. Oncogene 2003;22:8699
- Compared to frequency in bladder UC = **1%**
- **MSI associated with:**
  1. Ureteric tumours (38% vs. 8%)
  2. Female patients
  3. Low stage/grade
  4. Inverted/papillary growth pattern
  5. Better survival (37mo vs. 22 mo in ≥pT2 N0 M0 UTUC)

Hartmann et al. Cancer Res 2002; 62: 6796

Roupret et al. Urology 2005;65:1233



[CANCER RESEARCH 62, 6796–6802, December 1, 2002]

Advances in Brief

Frequent Microsatellite Instability in Sporadic Tumors of the Upper Urinary Tract[1]

Arndt Hartmann, Livia Zanardo, Tina Bocker-Edmonston, Hagen Blaszyk, Wolfgang Dietmaier, Robert Stoehr, John C. Cheville, Kerstin Junker, Wolf Wieland, Ruth Knuechel, Josef Rueschoff, Ferdinand Hofstaedter, and Richard Fishel[2]

Institute of Pathology, University of Regensburg, 93042 Regensburg, Germany [A. H., L. Z., H. B., W. D., R. S., R. K., F. H.]; Genetics and Molecular Biology Program, Kimmel Cancer Center, Department of Microbiology and Immunology, Thomas Jefferson University, Philadelphia, Pennsylvania 19107 [T. B-E., R. F.]; Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota [J. C. C.]; Department of Urology, University of Jena, Jena, Germany [K. J.]; Department of Urology, St. Josefs Hospital, Regensburg, Germany [W. W.]; and Institute of Pathology, Kassel, Germany [J. R.]

Oncogene (2003) 22, 8699–8706
© 2003 Nature Publishing Group All rights reserved 0950-9232/03 $25.00
www.nature.com/onc

Distinct patterns of microsatellite instability are seen in tumours of the urinary tract

James WF Catto*[,1,2], Abdel-Rahmene Azzouzi[1,2], Najla Amira[3], Ishtiaq Rehman[2], Kenneth M Feeley[4], Simon S Cross[5], Gaelle Fromont[6], Mathilde Sibony[7], Freddie C Hamdy[2], Oliver Cussenot[3] and Mark Meuth[1]

[1]The Institute for Cancer Studies, University of Sheffield, UK; [2]The Academic Urology Unit, University of Sheffield, UK; [3]CeRePP-EA3104, Département d'Urologie, Faculté de Médecine, Paris, France; [4]Department of Pathology, Royal Hallamshire Hospital, Sheffield, UK; [5]The Academic Pathology Unit, University of Sheffield, UK; [6]Service d'Anatomo-Pathologie, Institut Mutualiste de Montsouris, Paris, France; [7]Service d'Anatomo-Pathologie, Hôpital Tenon, Paris, France

Genetics vs. Epigenetics

Genetics = Information inherited on basis of nucleotide sequence

Epigenetics = Information inherited on basis of gene expression levels

Or:

Genetics = Blueprint for manufacture of all proteins necessary to create a living organism

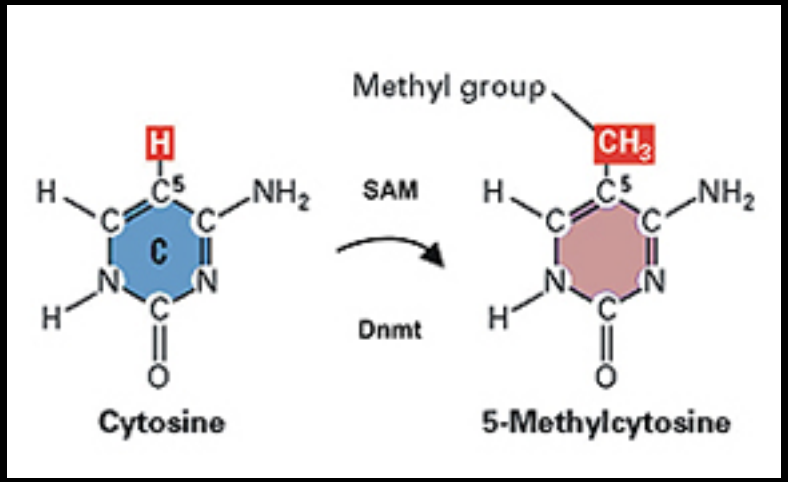
Epigenetics = Instructions on how, where and when the genetic information should be used

DNA methylation is an Epigenetic mechanism and is the only endogenous modification of DNA in mammals

DNA Methylation

A

T



C

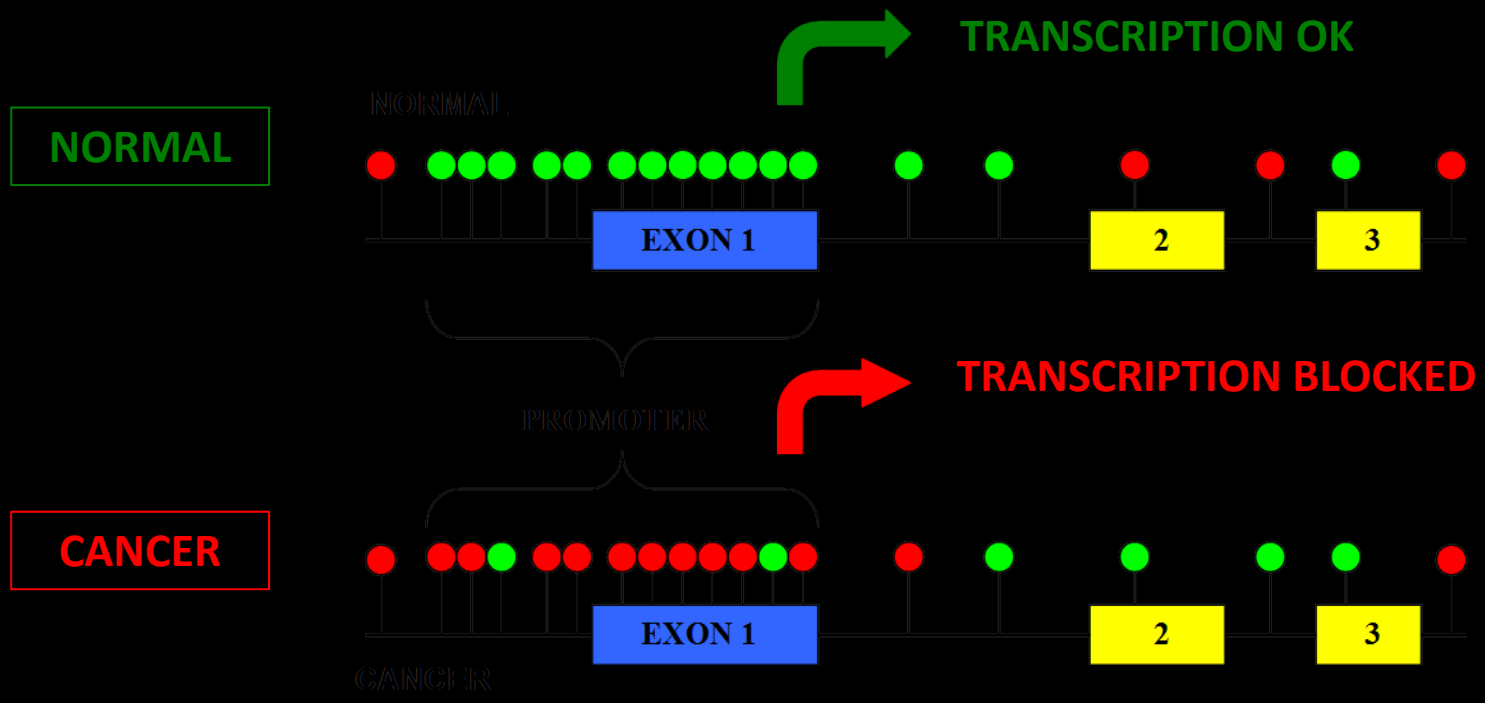
G

- 5-methylcytosine is the so-called "5th base"
- ONLY affects CpG dinucleotides
- You can still have unmethylated CpGs
- 5-methylcytosine accounts for 3-5% of cytosines in whole genome
- CpG clusters exist = "CpG Islands"
- DNA methylation has **physiological** and **pathological** roles

DNA Hypermethylation

- Pathological version of DNA methylation
- DNA hypermethylation refers to aberrant methylation patterns within ‘CpG islands’ of promoter regions that leads to silencing of expression of the associated gene
- This can have serious detrimental effects if the gene is a key functional gene e.g tumour suppressor gene

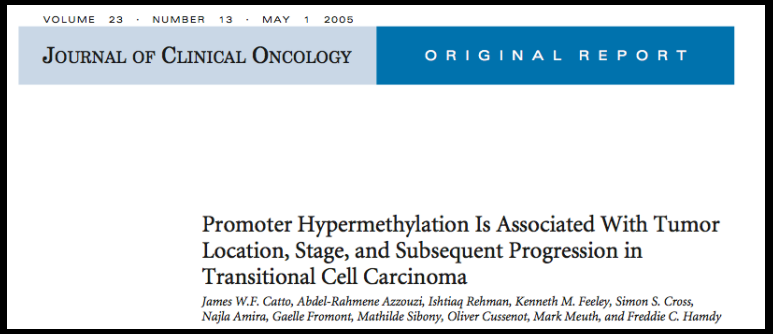
DNA Hypermethylation in Cancer



Methylation of TSG promoter leads to lack of expression and ability for uncontrolled cell malignant cell growth

Catto et al. J Clin Oncol 2005;23:2903-10

DNA Hypermethylation in UTUC



- 280 patients (117 bladder UC vs. 152 UTUC; RP 84 Ureter 68)
- 11 CpG Islands of key UC genes e.g p16, E-cadherin
- Overall, hypermethylation in UTUC = **94%** (vs. 76% bladder; p<0.0001)
- **% methylation greater in 10/11** islands for UTUC vs. bladder

Thus, frequency and extent of DNA hypermethlation greater in UTUC

Catto et al. J Clin Oncol 200;23:2903

HNPCC Syndrome

- **Hereditary Non-Polyposis Colorectal Cancer** Syndrome

- Autosomal dominant genetic disease with 80% lifetime risk of malignancy, mainly colon cancer but also endometrium, ovary, stomach, small bowel, skin, brain, hepatobiliary and UTUC

- Also known as Lynch Syndrome (described in 1966)

- Aetiology: Inherited defect (caused by **DNA hypermethylation**) in DNA mismatch repair system leading to **MSI**

x22 fold increased risk of UTUC

Watson et al. Anticancer Res 1994; 14:1635-9

HNPCC-associated UTUC

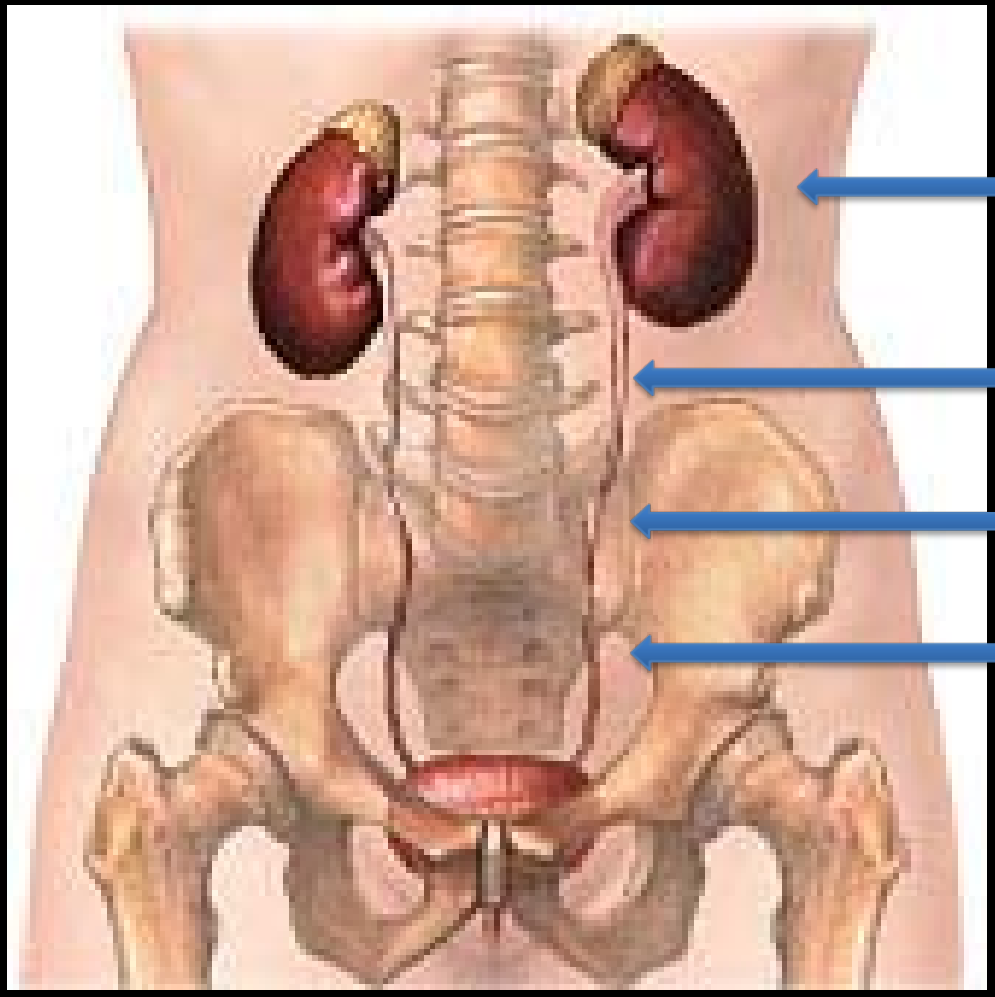
Whenever you see a new diagnosis of UTUC think HNPCC if:

1. Patient <60 years old
2. Personal history of HNPCC-associated cancer:
   COLON, endometrium, ovary, small bowel
3. First degree relative <50 with HNPCC-associated cancer
4. Two first degree relatives with HNPCC-associated cancer

Consider evaluation for other HNPCC-associated cancer and genetic counselling/testing

Roupret et al. Eur Urol 2008;54:1226-1236

Tumour Location in UUT



RENAL PELVIS: 60-70% overall

URETER: 30-40% overall

Upper Ureter: 5%

Mid Ureter: 25%

Lower Ureter: 70%

Tumour Location and Outcome

- Controversial

- **Worse outcome for ureter vs. renal pelvis**

  Classic thinking and secondary to:
  "Protective effect of renal parenchyma"
  "Extensive peri-ureteral lymphovascular tissue"
  "Lack of peri-ureteral fat layer"

  Park et al. J Urol 2009;182:894. Ouzzane et al. Eur Urol 2011;60:1258

- **Worse outcome for renal pelvis vs. ureter**

  "Thinner muscularis layer of renal pelvis"

  Van der Poel et al. Eur Urol 2005;48:438

No definitive conclusion can be made from data as large multi-institutional studies have not confirmed either way

Favaretto et al. Eur Urol 2010;58:574. Raman et al. Eur Urol 2010;57:1072

Clinical Prognosticators

YES	WEAK	NO
• **Location** • Smoking • Obesity • Hydronephrosis • Previous Bladder UC • Tumour size • URS Bx Grade • ASA score	• Age • ECOG-PS • Symptoms • Imaging stage	• Race • Gender
McLaughlin et al. Cancer Res 1992;52:254 Ehdaie et al. J Urol 2011;186:66 Cho et al. Urology 2007;70:662 Park et al. J Urol 2009;182:894 Mullerad et al. J Urol 2004;172:2177 Simone et al. BJU Int 2009;103:1052 Brien et al. J Urol 2010;184:69 Berod et al. BJU Int 2012 (in press)	Shariat et al. BJU Int 2010;105:1672 Martinez et al. BJU Int 2012;109:1155 Raman et al. Urol Oncol 2011;29:716 Scolieri et al. Urology 2000;56:930	Fernandez et al. Urology 2009;73:142 Matsumoto et al. BJU Int 2011;108:304

Vol. 177, 1715-1720, May 2007
Printed in U.S.A.
DOI:10.1016/j.juro.2007.01.030

Behavior of Urothelial Carcinoma With Respect to Anatomical Location

J. W. F. Catto,* D. R. Yates, I. Rehman, A. R. Azzouzi, J. Patterson, M. Sibony, O. Cussenot and F. C. Hamdy

From the Academic Urology Unit, University of Sheffield (JWFC, DRY, IR, FCH) and Department of Urology, Royal Hallamshire Hospital (JP), Sheffield, United Kingdom, and Service d'Urologie, Centre Hospitalier Universitaire d'Angers (ARA), Angers and Academic Urology (OC) and Pathology (MS) Departments, Hospital Tenon, Paris, France

- 425 patients (275 bladder vs. 150 UTUC; 67 ureter, 79 RP)
- Median follow-up 46mo (2-216)
- UTUC higher stage: 77% ≥ pT1 vs. 52% (p<0.001)
- UTUC higher grade: 86% ≥G2 vs. 79% (p=0.015)
- Stage and grade associated with outcome on M/A analysis
- **BUT no difference in outcomes between upper and lower tract tumours when stage and grade considered (p=0.4498)**

	UTUC	Bladder
Recurrence (%)	41	37
Progression (%)	44	40
Death from Cancer (%)	43	44

Pathological Prognosticators

Generic

- Stage (best)
- Grade
- Lymph node status
- Lymphovascular invasion
- Associated CIS
- Tumour Size

Novara et al. Cancer 2007;110:1715
Kondo et al. J Urol 2007;178:1212
Kikuchi et al. J Urol 2005;174:2120
Wheat et al. Urol Oncol 2012;30:252

More UTUC specific

- Multifocality
- Architecture
- Necrosis
- PSM

Keeley Jr et al. J Urol 1997;157:33
Langner et al. Vichows Arch 2006;448:604
Zigeuner et al. Eur Urol 2010;57:575
Colin et al. Ann Surg Oncol 2012;19:3613

Conclusion: Same or Different?

- Things that seem to suggest different:

① Specific genetic defects e.g microsatellite instability, DNA methylation
② Association with familial cancer syndrome e.g HNPCC
③ Unique risk factors e.g Balkans nephropathy

Upper Tract UC and Bladder UC are the same but different

- Things that seem to suggest same?

① Common risk factors e.g smoking and aromatic amines
② Urine flow and multifocality
③ No difference in outcomes when controlled for stage and grade
④ Clonality studies
⑤ Gene expression profiling

THANK YOU