The effect of urothelial cancer surveillance in Lynch syndrome

Perspective from a Danish urologist

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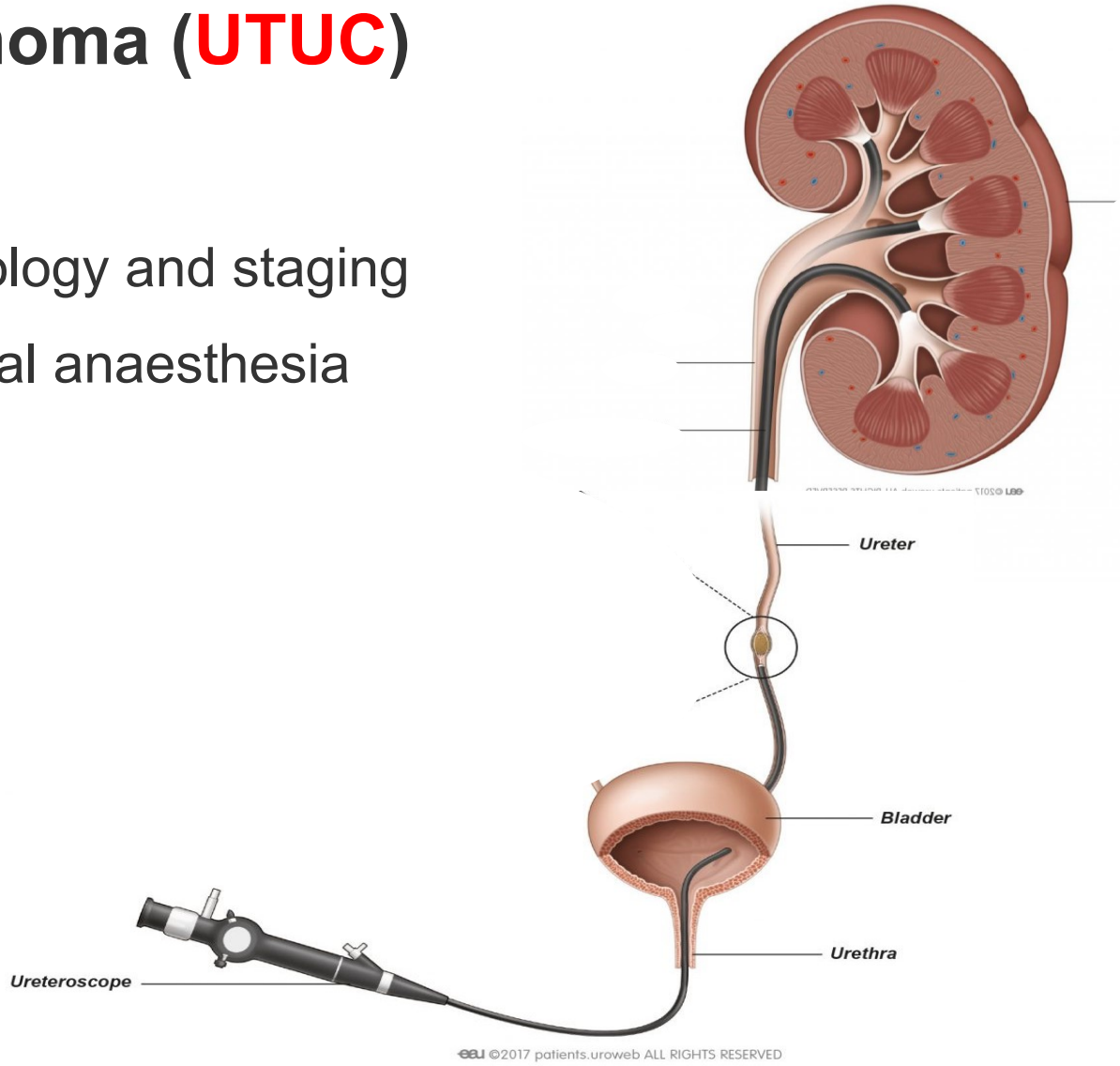
Upper tract urothelial carcinoma (UTUC)

- Rare disease
- Notoriously difficult to get good histology and staging
- Nephroureteroscopy requires general anaesthesia

- **Silent but deadly:**
  - Deadly to kidneys if local
  - Deadly to patients if advanced



The Danish way (new guidelines 2022)

- **Screening for UTUC in LS families**
  - ≥ 35 yrs from LS families w pathogenic MSH2 variant
  - ≥ 35 yrs from other LS families w at least 2 members w UTUC
  - Annual urine dipstick, urine cytology, ultrasound of kidneys
- **Screening for LS in UTUC patients**
  - Family history
  - IHC for MMR in tumor tissue from **all** new UTUC

- Does it work? Is it cost effective?
- What is the goal? Saving kidneys? Saving lives?

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  - Annual **urine dipstick, urine cytology, ultrasound of kidneys**
- Urine dipstick: 10% pos in healthy population
- Cytology: 0.1 % UTUC in LS population. 29% sensitivity in UTUC population.
- Ultrasound. Sensitivity unknown.

- Inform patients of which symptoms to react to in between screenings

Urine cytology or dipstick positive – what to do?

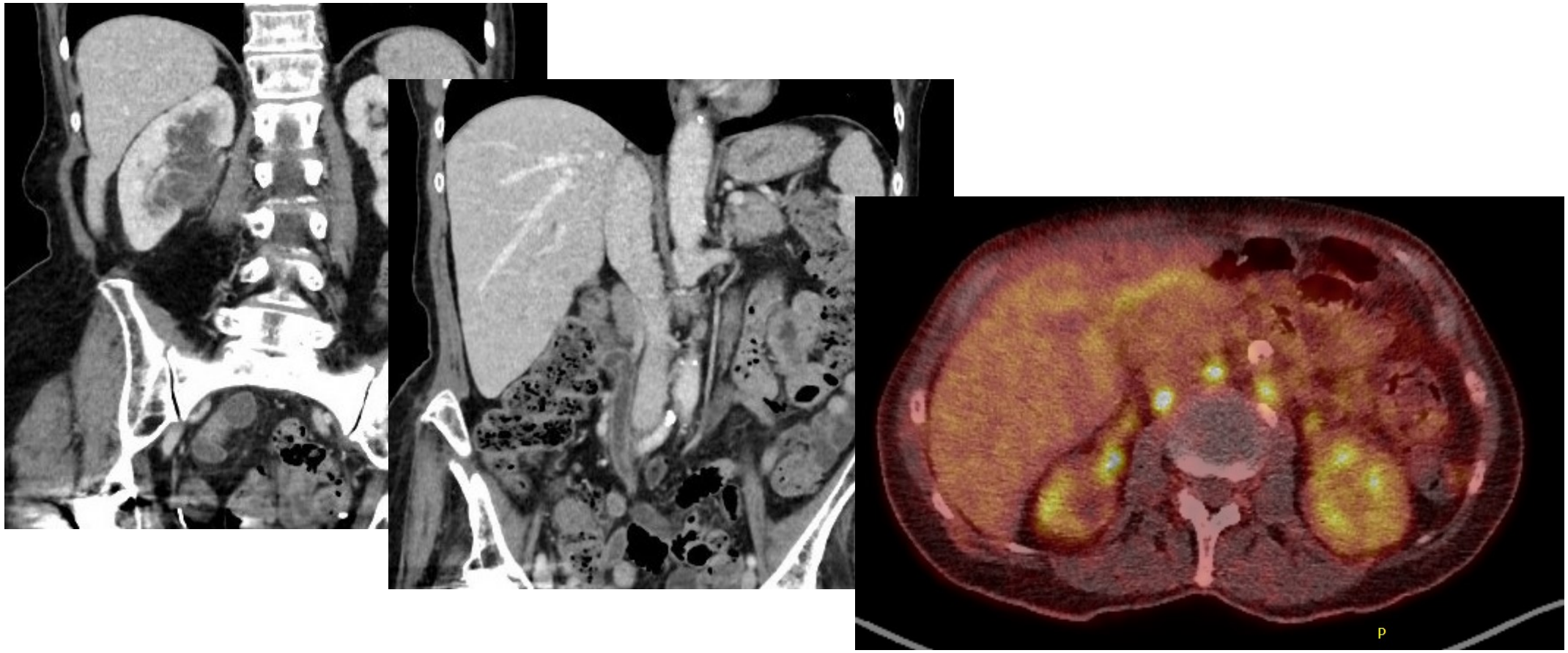
Is ultrasound meaningful?

Since 2023 at Rigshospitalet:

- Ultrasound if cytology and dipstick neg.
- Urine cytology positive – CT urography and cystoscopy
- Dipstick positive – CT urography

- When to repeat?

Patient case 1 – finding LS in new UTUC patient
Metastatic disease at diagnosis



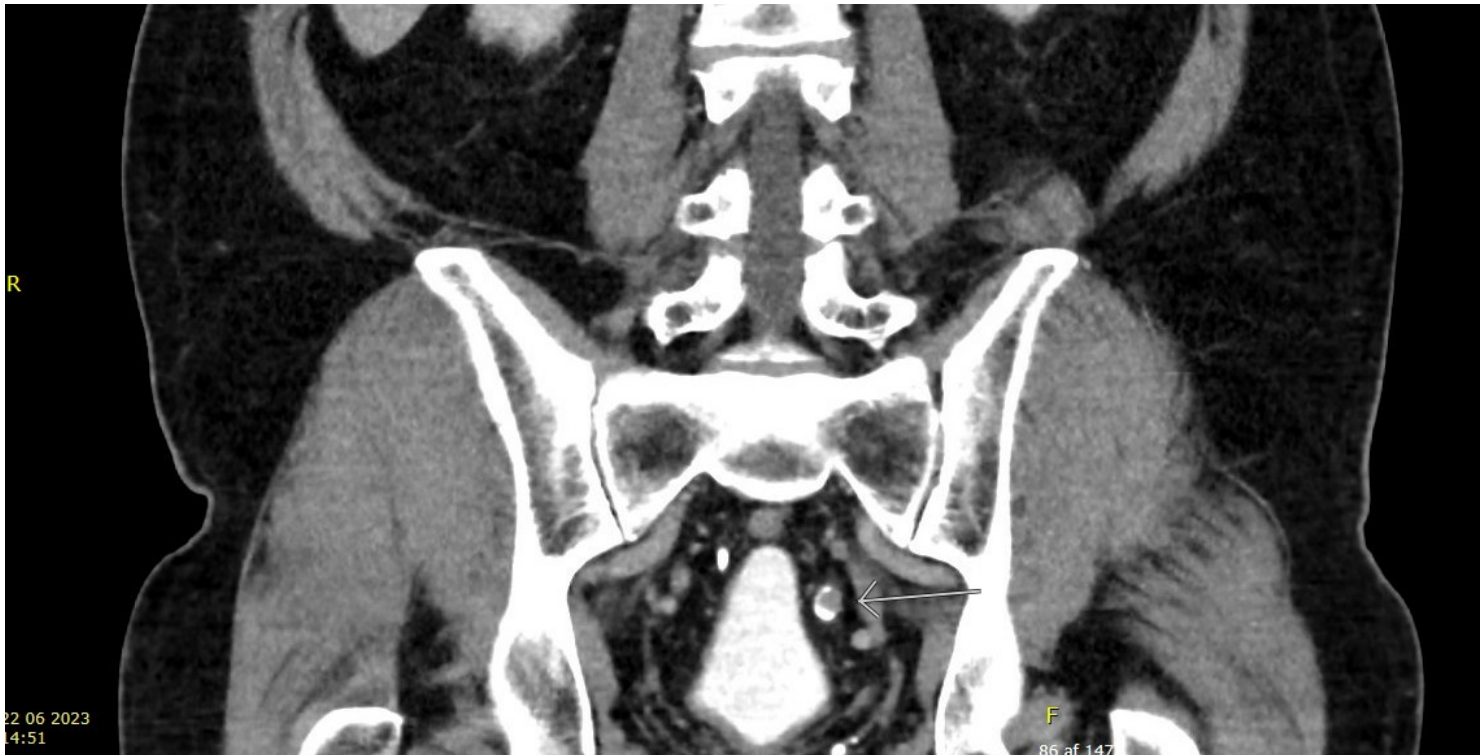
Patient case 2 – ideal screening outcome?

- 62-year old male
- Previous medical hx
  - Obesity, low grade diabetic nephropathy, colorectal cancer 2013, LS
- Previous surgical hx
  - Gastric bypass, total colectomy 2013, ileostomy, emergent cholecystectomy

- Lack of pMSH2/MSH6 in colon cancer tissue 2013- referred to the HNPCC registry

Patient case 2 – ideal screening outcome?

- 2022 offered screening for UTUC
- 2023 cytology negative, urinary dipstick positive
- CT urography: suspicion of tumor distal ureter



Patient case 2 – ideal screening outcome?

- Nephroureteroscopy 2023
- Histology from biopsy
  - Ta low grade, lack of pMSH2/MSH-6 expression

- Resection of distal ureter aug 2023
- Histology
  - Ta high grade. Free margins.

- Sept 2024: no recurrence.

EAU guidelines for follow-up after kidney-sparing treatment

Recommendations	Strength rating
After radical nephroureterectomy	
Low-risk tumours	
Perform cystoscopy at three months. If negative, perform subsequent cystoscopy 9 months later and then yearly, for 5 years.	Weak
High-risk tumours	
Perform cystoscopy and urinary cytology at 3 months. If negative, repeat subsequent cystoscopy and cytology every 3 months for a period of 2 years, and every 6 months thereafter until 5 years, and then yearly.	Weak
Perform computed tomography (CT) urography and chest CT every 6 months for 2 years, and then yearly.	Weak
After kidney-sparing management	
Low-risk tumours	
Perform cystoscopy and CT urography at 3 and 6 months, and then yearly for 5 years.	Weak
Perform ureteroscopy (URS) at 3 months if no second-look ureteroscopy was performed.	Weak
High-risk tumours	
Perform URS and urinary cytology *in situ* at 3 and 6 months.	Weak

Principles for screening – are they met?

- Specific disease : UTUC 👍
- Primary prevention not possible 👍
- Important health problem 👍
- Simple, safe, precise and validated screening test (shaky ground) 👎
- Effective intervention – but does early intervention give better outcomes? 👍
  Does screening programme reduce mortality or morbidity?
- Cost effective? 👎
- Plan for managing and monitoring the screening programme and an agreed set of quality assurance standards – in the making?

Urine-based tests for non-muscle invasive bladder cancer (NMIBC)

Soon in DK guidelines for NMIBC follow up?

- Goals NMIBC
  - Reduce invasive procedures (pain, UTI)
  - Reduce false positive cystoscopies
  - Reduce costs
  - Reduce time/cost on healthcare providers, patients?
- Goals Lynch screening
  - Reduce radiation dose from CT urography
  - Detect UTUC??

Non-invasive urine-based tests - examples

- "Uromonitor" for detecting NMIBC recurrence in 202 patients (Azawi et al. Cancers 2023)
  - rtPCR assay of hotspot mutations in TERT, FGFR3
  - Sensitivity 90%, specificity 96% (cystoscopy gold standard)
  - 3 patients w UTUC found – proof of concept
- "Xpert bladder cancer monitor"
  - mRNA from 5 genes
  - Current RCT: urine test vs. cystoscopy!
- Others: Cx-Bladder, ADX-BladderTM, EpiCheck, …

- Non-invasive test development, no more ultrasound or CT urography
  - Patient perspective
  - Burden on healthcare systems
  - Economic perspective

Lynch syndrom (LS)*				
Patogen variant i	*MLH1*	*MSH2*	*MSH6*	*PMS2*
Urologisk screeningsprogram og behandling				
Cancerrisiko	4% (kvinder) 5% (mænd)	19% (kvinder) 18% (mænd)	6% (kvinder) 2% (mænd)	4% (begge køn)
Screeningsprogram	Urinanalyse for blod, urincytologi og UL-scanning af nyrerne årligt			
	Kun i familier med mindst to personer med øvre invasive eller ikke-invasive uroteliale tumorer	Alle risikopersoner	Kun i familier med mindst to personer med øvre invasive eller ikke-invasive uroteliale tumorer	Kun i familier med mindst to personer med øvre invasive eller ikke-invasive uroteliale tumorer
Alder for opstart	35 år			
Kirurgisk behandling	Endoskopisk lokalbehandling eller radikal nefroureterektomi tilbydes Nyrebevarende lokalbehandling bør tilstræbes			