Epidemiology

• Urothelial carcinomas are the 4th most common tumours after prostate (or breast), lung & CRC (1,2).

• UTUC are uncommon & account for
  – ~5% of urothelial cell carcinomas &
  – 5-8% of all renal tumours (3).

• Incidence of synchronous bilateral UTUC is ~ 3%.

Epidemiology

- Annual incidence of UTUCs in Western countries is ~ 2 new cases per 100,000 inhabitants.
- Pyelocaliceal tumours ~ twice as common as ureteral tumours.
- In 17% of cases, concurrent bladder ca is present (1).
- Recurrence of ds in the bladder occurs in 22-47% of UTUC pts (2-4), whereas recurrence in the contralateral UT is observed in 2-6% (5-6).

In Malaysia

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National Cancer Registry Report 2007, Ministry of Health Malaysia
### Ten most frequent cancers, males, Malaysia 2007

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### Ten most frequent cancers, females, Malaysia 2007

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<td>C53</td>
<td>Cervix Uteri</td>
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<td>Ovary</td>
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<td>Stomach</td>
<td>279</td>
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</tbody>
</table>
Epidemiology

• The natural history of UTUCs differs from that of bladder ca:
  – 60% of UTUCs are invasive at dx compared with only 15-25% of bladder ca (1,2).

• UTUCs
  – peak incidence 70s and 80s
  – 3 times more common in men than in women (3,4).

Epidemiology

• There are familial/hereditary cases of UTUCs linked to hereditary non-polyposis colorectal carcinoma (HNPCC) (1).

• Among pts with UTUCs, HNPCC can be screened during a medical interview (2).


Epidemiology

• There is a suspicion of hereditary UTUC if the pt is
  – < 60 y/o,
  – has a personal h/o an HNPCC assc cancer,
  – a 1\textsuperscript{st} degree relative aged < 50 years with HNPCC-assc cancer, or
  – two 1\textsuperscript{st} degree relatives with HNPCC-assc cancer (1).

• These pts should undergo DNA sequencing to identify hereditary cancers that have been misclassified as sporadic cancers by insufficient clinical data (2).

Figure 3.1: Selection of patients with UTUC for hereditary screening from first medical interview

UTUC

Systematic screening during medical interview

Suspicion of hereditary UTUC (10-20%)
- Age < 60 yr
- Personal history of HNPCC-spectrum cancer
  - First degree relative < 50 yr with HNPCC-spectrum cancer
  - Two first-degree relatives with HNPCC-spectrum cancer

Sporadic UTUC (80-90%)

Germ-line DNA sequencing: mutation

- Clinical evaluation for other HNPCC-related cancer: colorectal, gastrointestinal, endometrial ovarian and skin
  - Close monitoring and follow-up
  - Familial genetic counselling

HNPCC = hereditary non-polyposis colorectal carcinoma.
Risk Factor
Risk Factors

• Many environmental factors contribute to the dev of UTUCs (1).

• Some are similar to those assc with bladder ca, whereas others are more specific for UTUC.

• Principal exogenous risk factors:
  – tobacco &
  – occupational exposure

Risk Factors

• Tobacco exposure increases the relative risk of developing UTUC from 2.5 to 7 (1).

Risk Factors

• UTUC ‘amino’ tumours’ are related to occupational exposure to certain aromatic amines.
  – These aromatic hydrocarbons are used in many industries (e.g. dyes, textiles, rubber, chemicals, petrochemicals and coal).
  – benzidine and b-naphthalene (carcinogen)
  – banned since the 1960s in most industrialized countries

• In most cases, UTUCs are 2° to an amino tumour of the bladder.
Risk Factors

• To develop a UTUC,
  – the average duration of exposure needed is ~ 7 years
  – latency period of about 20 years following termination of exposure.

• Odds ratio of developing UC after exposure to aromatic amines is 8.3 (1).

• UTUC resulting from phenacetin consumption almost disappeared after the product was banned in the 1970s (1).

Risk Factors- Specific to UTUC

• Congenital
  – HNPCC

• Acquired
  – Balkans nephropathy
  – Chinese herb nephropathy
Congenital

Review – Urothelial Cancer

Upper Urinary Tract Urothelial Cell Carcinomas and Other Urological Malignancies Involved in the Hereditary Nonpolyposis Colorectal Cancer (Lynch Syndrome) Tumor Spectrum

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b Institute for Cancer Studies and Academic Urology Unit, Royal Hallamshire Hospital, University of Sheffield, Sheffield, United Kingdom
Upper Urinary Tract Urothelial Cell Carcinomas and Other Urological Malignancies Involved in the Hereditary Nonpolyposis Colorectal Cancer (Lynch Syndrome) Tumor Spectrum

Context: The data describing the urologic extracolonic cancers associated with hereditary nonpolyposis colorectal cancer (HNPCC) are variable.

Objective: Provide an update about the current urologic tumor spectrum in HNPCC.

Evidence acquisition: Data on HNPCC extracolonic tumor spectrum published in the literature were analysed using MEDLINE with emphasis on urological malignancies, upper tract tumors, clinical criteria, genetic diagnosis and counselling.

Evidence synthesis: HNPCC is a form of colorectal cancer with a dominant autosomal mode of inheritance. HNPCC is caused by germ-line mutations affecting one or several mismatch repair genes. Cancers other than colorectal cancer are sometimes associated with HNPCC. These include specific urological malignancies, most notably tumors of the upper urinary tract, which have been reported to occur at a rate ×22 higher than the general population. Upper urinary tract tumors rank third (5%) after colon (63%) and endometrial (9%) cancer within the group of HNPCC related tumors. Prostate cancer and testicular germ cell tumors are rarely associated. Due to lack of appreciation of such hereditary associations, some inherited cancers are still misclassified as sporadic and their incidence is underestimated. The biological tests requested in suspected cases of HNPCC are: microsatellite instability (MSI) analysis, immunohistochemistry and DNA sequencing. When gene mutations are detected, the patient and their family will benefit from a multidisciplinary management approach. The presence of other HNPPC-associated cancers is sought and close monitoring of patients is undertaken. Genetic counselling is provided to the patient’s family.

Conclusions: The recognized urologic tumor spectrum in HNPCC includes upper tract tumors. However, in order not to overlook a hereditary cancer, urologists should be aware of the possible urological malignancies associated with HNPCC (i.e., prostate and testicular carcinomas) and evaluate appropriately anyone they feel are at high risk of underlying HNPCC based on set clinical criteria.

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Amsterdam criteria for the clinical diagnosis of HNPCC (all need to be fulfilled)

Amsterdam Criteria I (1991)
1. One member diagnosed with colorectal cancer before age 50.
2. Two affected generations.
3. Three affected relatives, one of them a first degree relative of the other two.
4. Familial adenomatous polyposis should be excluded.
5. Tumors should be verified by pathological examination.

Amsterdam Criteria II (1999)
1. There should be at least three relatives with an HNPCC-associated cancer (colorectal cancer, cancer of the endometrium, small bowel, ureter, or renal pelvis).
2. One should be a first degree relative of the other two.
3. At least two successive generations should be affected.
4. At least one should be diagnosed before age 50. Familial adenomatous polyposis should be excluded in the colorectal cancer cases.
5. Tumors should be verified by pathological examination.
Flow-chart for the management of a urological malignancy suspected to be part of the HNPCC (Lynch) syndrome.
Risk Factors- Specific to UTUC

• Congenital
  – HNPCC

• Acquired
  – Balkans nephropathy
  – Chinese herb nephropathy
Balkan endemic nephropathy

- BEN - a familial chronic tubulo-interstitial ds w a slow progression to terminal renal failure, affects people living in the alluvial plains along the tributaries of the Danube River.

The Balkans are generally considered to include, in whole or in part, Albania, Bosnia and Herzegovina, Bulgaria, Croatia, Greece, Kosovo, the Republic of Macedonia, Montenegro, Serbia, Slovenia, and the European part of Turkey.
Balkan endemic nephropathy

• General features of BEN:
  – A slowly progressive chronic tubulointerstitial disease that presents insidiously with signs of uremia during the 5th or 6th decade of life
  – almost exclusively in farmers
  – often affecting multiple family members in a given household
  – M:F distribution is equal.
  – typically effects those who have lived in an endemic area for >20 years.
  – Individuals who leave an endemic area before age 20 are spared, whereas immigrants are likely to develop the disease 15–20 years after settling in an endemic area, regardless of race or ethnicity.
Balkan endemic nephropathy

• Clinically, the ds is characterized by tubular proteinuria, usually β2-microglobulinuria, profound anemia, and absence of HPT & edema.

• When investigated early during its evolution, overt renal disease is preceded by tubular dysfunction,
  – including salt wasting, Fanconi syndrome (i.e., amino aciduria, renal tubular acidosis, glycosuria, uricosuria), and tubular proteinuria.
Balkan endemic nephropathy

• Urinalysis is usually unremarkable; RBCs & casts are often absent.

• One hallmark of BEN is **LMW proteinuria**;
  – among LMW urinary proteins, detection of **β2-microglobulin** in the urine has been found to be useful for identifying new cases of BEN and tracking both BEN suspects and pts at risk.

• Histologically,
  – paucity of inflammatory cell infiltration,
  – extensive and severe fibrosis,
  – tubule atrophy
Balkan endemic nephropathy

• In advanced stages the kidneys are dramatically reduced in size, to as small as 2–3 cm, with smooth contours.
• Nearly half of affected pts also eventually develop papillary TCCs in the renal pelvis & the ureters.
Upper urothelial carcinoma in Balkan endemic nephropathy and non-endemic regions: A comparative study of pathological features

Ljubinka Jankovic Velickovic\textsuperscript{a}, Takanori Hattori\textsuperscript{b}, Zana Dolicanin\textsuperscript{a}, Milan Visnjic\textsuperscript{c}, Miljan Krstic\textsuperscript{a}, Ivan Ilic\textsuperscript{a}, Rade Cukuranovic\textsuperscript{d}, Milena Rajic\textsuperscript{e}, Vladisav Stefanovic\textsuperscript{d,}\textsuperscript{*}

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\textsuperscript{c}Faculty of Medicine, Clinic of Surgery, Nis, Serbia
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Received 15 July 2008; received in revised form 1 September 2008; accepted 8 September 2008

Abstract

Upper urothelial carcinoma (UUC), a rare neoplasm, occurs more frequently in some regions of Balkan countries than in other areas in the world. The aim of this study is to compare phenotypic morphological characteristics of UUC in Balkan endemic nephropathy (BEN) region and control rural and city populations free of BEN, and to determine the characteristic(s) that could discriminate tumors in endemic and non-endemic regions. The authors analyzed biopsies from 88 patients with UUC, 40 patients who live in Balkan endemic (BEN) settlements and 48 control subjects. The histological sections were used to assess morphological variables: histologic grade, pathologic stage (pT), growth pattern, pattern of invasion, lympho-vascular invasion (LVI), presence of necrosis and metaplastic changes (squamous or glandular) within the tumor. Statistically significant differences between the groups were found concerning tumor grade, pattern of invasion, growth pattern and metaplastic changes. High-grade tumors and trabecular/infiltrative patterns of invasion were more frequent in the group of BEN tumors ($\chi^2 = 4.583$, $p < 0.05$). Moreover, solid growth and metaplastic changes are significant in BEN tumor, $\chi^2 = 9.696$, $p < 0.01$; $\chi^2 = 9.35$, $p < 0.01$, respectively. Discriminant analysis of morphological variables had indicated that BEN and control tumors are significantly different (Wilks' lambda = 0.833, $\chi^2 = 15.044$ and $p < 0.05$). The best characteristic that differentiated them was growth pattern; i.e., solid growth for BEN tumors and papillary for control tumors.
Risk Factors- Specific to UTUC

- Congenital
  - HNPCC

- Acquired
  - Balkans nephropathy
  - Chinese herb nephropathy
Chinese herb nephropathy

• Several studies have revealed the carcinogenic potential of aristolochic acid contained in
  – *Aristolochia fangchi* &
  – *Aristolochia clematis* (plants endemic to the Balkans)
• Contain a set of **highly toxic nitrophenolate** derivatives that exhibit a powerful mutagenic action due to their ability to make up covalent links with cell DNA.
• Its derivative d-aristolactam causes a specific **mutation in the p53 gene** at codon 139.
Aristolochia fangchi

广防己
Aristolochia clematitis

Herbaceous, perennial; stem erect, glabrous, zigzag, striate, 1-2 ft tall. Leaves dark green, reniform, subacute or obtuse at the apex, glabrous or their margins minutely pubescent-ciliolate, strongly reticulate-veined, 2-5 in wide; petioles shorter than the blades. Flowers fascicled in the axils, 1"-1½" long; tube of the calyx yellowish green, straight, enlarged around the ovary, the 6 lobes appendaged; anthers equidistant.

Occupational Exposure to Herbs Containing Aristolochic Acids Increases the Risk of Urothelial Carcinoma in Chinese Herbalists

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Abbreviations and Acronyms
AA = aristolochic acid

Accepted for publication June 22, 2012. Study received approval from the National Taiwan University College of Public Health ethics review committee.

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Purpose: Aristolochic acid can cause urothelial carcinoma. Herbal remedies containing aristolochic acids were previously categorized as proven group 1 human carcinogens by the WHO cancer agency, the International Agency for Research on Cancer. However, the health effect on workers exposed to aristolochic acid is unclear. Fangchi, a representative herb containing aristolochic acid, is commonly used in the Chinese herbal medicine industry. We determined whether workers exposed to fangchi are at increased risk for urothelial carcinoma.

Materials and Methods: We designed a case-control study based in a national representative cohort of Chinese herbalists. This study analyzed 6,564 Chinese herbalists employed between 1985 and 1998. All incident cases of urothelial carcinoma that occurred between 1988 and 2001 were defined as the case group. Controls were selected from the baseline cohort in a randomized manner. A total of 24 cases and 140 controls were included in analysis. Information about fangchi exposure was obtained in a questionnaire survey administered in 2002.

Results: Processing, selling or dispensing herbs containing fangchi significantly increased the risk of urothelial carcinoma (HR 2.4, 95% CI 1.1–5.3, p = 0.03). This relationship was independent of cigarette smoking or potential arsenic exposure from drinking water from deep wells.
Risk Factors

• Certain **genetic polymorphisms** are a/w an increased risk of ca or faster ds progression, which introduces variability in the inter-individual susceptibility to the risk factors.

• Only two polymorphisms specific to UTUC have been reported so far (1,2).
  
  – A variant allele, SULT1A1*2, which reduces sulfotransferase activity, and a polymorphism located at the T allele of rs9642880 on chromosome 8q24 enhance the risk of developing UTUC.


Prognostic Factors in Cancer
Prognostic factors

- UTUCs that invade the muscle wall usually have a very poor prognosis.
- The 5-year specific survival is
  - < 50% for pT2/pT3
  - < 10% for pT4 (1,2)

Prognostic factors

• Tumour stage and grade
  – The primary recognized prognostic factors are tumour stage and grade (1-3).
  – Extranodal extension appears to be a powerful predictor of clinical outcomes in patients with UTUCs and positive lymph node metastases (4).


Prognostic factors

Age and sex

• Sex - not considered an independent prognostic factor that influences UTUC mortality (1).
• Age - considered to be an independent prognostic factor because older age at the time of RNU is a/w decreased CSS (2) (LE: 3).
• Chronological age alone should not be an absolute exclusion criterion for the tx of potentially curable UTUC, but rather overall life expectancy.
  – A significant proportion of elderly pts can still be cured with RNU, suggesting chronological age alone is an inadequate indicator of outcomes in older UTUC patients (2,3).

Prognostic factors

Ethnicity

• African American have worse outcomes compared to other races.

Prognostic factors

• Tumour location
  – The initial location of the tumour within the UUT (e.g. ureter vs. renal pelvis) is a prognostic factor (1-3) (LE: 3)
  • After adjustment for tumour stage, ureteral and multifocal tumours have a worse prognosis than renal pelvic tumours (2-4).

Prognostic factors

Tobacco consumption

- Smoking intensity (long-term exposure) & being a smoker at diagnosis increases the risk for poor oncological outcomes (1-3) (LE: 3).

Prognostic factors

Surgical waiting time

• A delay between dx and tumour removal may increase the risk of ds progression.
• The cut-off for removal is controversial and ranges between 30 days and 3 mths.
Prognostic factors

Lymphovascular invasion

- LVI is present in ~ 20% of UTUCs and is an independent predictor of survival (1,2).
- LVI status should be systematically included and specifically reported in the HPE (1,3) (LE: 3).

Prognostic factors

Surgical margins

• +ve surgical margin after RNU appears to be a significant factor for developing subsequent UTUC metastases (LE: 3).

• Pathologists should look for, and report on +ve margins at the level of the ureteral transection, bladder cuff, and around the tumour if the tumour is > T2 (1).

Other factors

• Extensive tumour necrosis * is an independent predictor of clinical outcomes in pts who undergo RNU.
  – * > 10% of the tumour area (1,2) (LE: 3).

• Tumour architecture (e.g. papillary vs. sessile) of UTUCs appears to be a/w the prognosis after RNU.
  – A sessile growth pattern is a/w the worst outcomes (3,4) (LE: 3).

---


Prognostic factors

- Presence of concomitant CIS in pts w organ-confined UTUC is a/w a higher risk of recurrent ds & CS mortality (1,2) (LE: 3).
  - Similar to lower tract UC, concomitant CIS is an independent predictor of worse outcomes in organ confined ds (3).

Prognostic factors

- A previous hx of bladder CIS is a/w increased risk of recurrence and death from UTUCs.

- The ASA score also significantly correlates with CSS after RNU (1), but ECOG performance status correlates only with OS (2).

- Obesity and higher BMI adversely affect cancer-specific outcomes in pts w UTUCs (3) (LE: 3).

### Prognostic factors

#### Molecular markers
- Several studies have investigated the prognostic impact of various tissue-based markers related to cellular processes, such as
  - cell adhesion (E-cadherin and CD24),
  - cell differentiation (Snail and epidermal growth factor receptor),
  - angiogenesis (hypoxia-inducible factor-1α and metalloproteinases),
  - cell proliferation (Ki67),
  - epithelial–mesenchymal transition (snail),
  - mitosis (Aurora-A),
  - apoptosis (Bcl-2 and survivin)
  - vascular invasion (récepteur d’origine nantais, RON) and
  - c-met protein (MET) (1-3).
- However, because of the rarity of the ds, the main limitations shared by these studies are their retrospective nature and their small sample size.

Prognostic factors

• MSI is an independent molecular maker used for tumour prognosis (1).
  — MSI can help detect germ-line mutations, allowing for the detection of possible hereditary cancers.

• To date, none of the markers has fulfilled the clinical and statistical criteria necessary to support their introduction in daily clinical decision making.

## Summary of preop/clinical prognostic factors in pts with UTUC

<table>
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<th>Markers</th>
<th>Comment</th>
<th>Level of evidence</th>
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<tbody>
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<td><strong>Patient characteristics</strong></td>
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<tr>
<td>Age</td>
<td>Advanced age is an independent predictor of worse CSS, RFS, and OS.</td>
<td>3</td>
</tr>
<tr>
<td>Race</td>
<td>Black non-Hispanic patients have worse survival relative to other racial groups.</td>
<td>3</td>
</tr>
<tr>
<td>ECOG-PS</td>
<td>ECOG-PS ≥1 is an independent predictor of worse OS.</td>
<td>3</td>
</tr>
<tr>
<td>Obesity</td>
<td>Body mass index ≥30 is an independent predictor of worse CSS, RFS, and OS.</td>
<td>3</td>
</tr>
<tr>
<td>Smoking status</td>
<td>Smokers are more likely to be diagnosed with UTUC and have higher cancer-specific mortality and bladder recurrence rates.</td>
<td>3</td>
</tr>
<tr>
<td><strong>Disease characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor location</td>
<td>According to several studies, ureteral location is an independent predictor of worse cancer control outcomes.</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Conversely, other studies showed that after adjustment for tumor stage, tumor location is no longer a predictor of CSS.</td>
<td></td>
</tr>
<tr>
<td>Clinical grade</td>
<td>Higher clinical (biopsy-determined) grade is a predictor of advanced pathologic tumor stage.</td>
<td>3</td>
</tr>
<tr>
<td>Hydronephrosis</td>
<td>Presence of hydronephrosis is an independent predictor of lower progression-free and cancer-specific survival rates.</td>
<td>3</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Systemic symptoms are associated with advanced tumor stage and grade.</td>
<td>3</td>
</tr>
<tr>
<td>Previous/synchronous bladder cancer</td>
<td>The presence of a previous or synchronous bladder cancer is an independent predictor of lower RFS and CSS rates.</td>
<td>3</td>
</tr>
</tbody>
</table>
Summary of postop/pathologic prognostic factors in pts with UTUC

<table>
<thead>
<tr>
<th>Markers</th>
<th>Comment</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pathologic tumor stage</td>
<td>Advanced pT stage is an independent predictor of worse cancer control outcomes.</td>
<td>3</td>
</tr>
<tr>
<td>Pathologic tumor grade</td>
<td>Higher tumor grade is an independent predictor of lower CSS rates. Both the 1973 and the 2004 WHO classifications of tumor grade independently predict cancer control outcomes.</td>
<td>3</td>
</tr>
<tr>
<td>Concomitant CIS</td>
<td>Concomitant CIS is associated with advanced tumor stage and grade and is an independent predictor of lower RFS and CSS rates.</td>
<td>3</td>
</tr>
<tr>
<td>LNI</td>
<td>The presence of LNI is an independent predictor of lower CSS rates.</td>
<td>3</td>
</tr>
<tr>
<td>Tumor multifocality</td>
<td>The presence of multifocal tumors is an independent predictor of lower CSS rates.</td>
<td>3</td>
</tr>
<tr>
<td>Tumor architecture</td>
<td>A sessile growth pattern is an independent predictor of lower progression-free survival, RFS, and CSS rates.</td>
<td>3</td>
</tr>
<tr>
<td>Tumor size</td>
<td>Larger tumor size is an independent predictor of lower progression-free survival and RFS rates.</td>
<td>3</td>
</tr>
<tr>
<td>LVI</td>
<td>The presence of LVI is associated with advanced tumor stage/grade and is an independent predictor of lower RFS and CSS rates.</td>
<td>3</td>
</tr>
<tr>
<td>Tumor necrosis</td>
<td>According to several studies, the presence of extensive tumor necrosis is associated with advanced tumor stage and is an independent predictor of lower RFS and CSS rates.</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>A recent multi-institutional study did not confirm the prognostic role of tumor necrosis after adjustment for tumor stage and other tumor characteristics.</td>
<td></td>
</tr>
</tbody>
</table>
Summary
Summary

• UTUC are uncommon
  – ~5% of UCC, 5-8% of all renal tumours
  – synchronous bilateral UTUC is ~ 3%
  – concurrent bladder ca ~17%
  – M>W
  – 70s – 80s

• Risk factors
  – Environmental - tobacco, occupation
  – Congenital - HNPCC
  – Acquired – BEN, Chinese herb nephropathy
Upper tract urothelial carcinoma - Prognostic factors

UTUC

Prognostic factors

Pre-operative

- size > 3 cm
- multifocality
- grade (biopsy, cytology)
- advanced age
- tobacco consumption
- distal ureter management
- ECOG- PS ≥ 1
- co-morbidity (ASA score)
- systemic revealing symptoms
- hydronephrosis
- delay surgery > 3 months
- tumour location
- African race
- BMI > 30
- gender

Major impact on survival

- stage
- grade
- carcinoma in situ
- bladder cuff excision
- lymphovascular invasion
- lymph node involvement
- tumour architecture
- positive surgical margins
- tumour necrosis
- molecular marker
- histological variant

Post-operative

Minor impact on survival

ASA = American Society of Anesthesiologists; BMI = body mass index; ECOG = Eastern Cooperative Oncology Group.
Thank you
Table 4.1: TNM classification 2009 for upper tract urothelial carcinoma

<table>
<thead>
<tr>
<th>T - Primary tumour</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
</tr>
<tr>
<td>T0</td>
</tr>
<tr>
<td>Ta</td>
</tr>
<tr>
<td>Tis</td>
</tr>
<tr>
<td>T1</td>
</tr>
<tr>
<td>T2</td>
</tr>
<tr>
<td>T3</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>T4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N - Regional lymph nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
</tr>
<tr>
<td>N0</td>
</tr>
<tr>
<td>N1</td>
</tr>
<tr>
<td>N2</td>
</tr>
<tr>
<td>N3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>M - Distant metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
</tr>
<tr>
<td>M1</td>
</tr>
</tbody>
</table>
# ECOG Performance Status

Developed by the Eastern Cooperative Oncology Group, Robert L. Comis, MD, Group Chair.*

<table>
<thead>
<tr>
<th>GRADE</th>
<th>ECOG PERFORMANCE STATUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease performance without restriction</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled; cannot carry on any selfcare; totally confined to bed or chair</td>
</tr>
<tr>
<td>5</td>
<td>Dead</td>
</tr>
</tbody>
</table>

Figure 6.2: Risk stratification of upper tract urothelial carcinoma

UTUC

Low-risk UTUC*:
- Unifocal disease
- Tumour size < 1 cm
- Low-grade cytology
- Low-grade URS biopsy
- No invasive aspect on MDCT-urography

High-risk UTUC**:
- Hydronephrosis
- Tumour size > 1 cm
- High-grade cytology
- High-grade URS biopsy
- Multifocal disease
- Previous radical cystectomy for bladder cancer

* All of these factors need to be present
** Any of these factors need to be present

MDCT = multidetector-row computed tomography; URS = ureterorenoscopy.