Bladder Cancer
1. Epidemiology

- Bladder cancer 25:100,000
- Prostate cancer 60-80:100,000
- Renal cancer 10:100,000
- Testicular cancer 6:100,000
- Males – Fourth commonest (8% of all cancers)
- Females – Ninth commonest (3% of all cancers)
- 10,000 cases each year
- 4300 deaths annually
- Decreasing Incidence
2. Aetiology

- **Smoking**
  - X2-5 higher incidence compared with non-smokers
  - Directly responsible for 60% of male and 25% of female TCC
  - Ex-smokers decrease risk – 60% reduction in risk by 25 years after cessation, but never to zero (Brennan Int J Cancer 2000)
  - Tobacco Carcinogens
    - 2-naphthylamine
    - 4-aminobiphenyl nitrosamines
  - Dose Dependant: ↑ risk if smoke more and for longer
  - Detoxification via Acetylation / Activation via Methylation

- **Occupational**
  - Second most important RF
  - Accounts for 25% of all cancers
  - Petrochemical Carcinogens:
    - Benzene Derivatives
    - Arylamines (2-Naphthylamine, 4-4 ABP)
2. Aetiology

- **Analgesics**
  - Phenacetin
    - Chemical structure similar to aniline dyes
    - Carcinogen described in 1987
    - 5-15kg over 10yrs = Increased risk for TCC

- **Infection**
  - Chronic cystitis + IDC + calculi increase risk of SCC
  - 2-10% of paraplegics with IDC
  - Chronic Inflammation increases risk of development of SCC bladder
  - Schistosoma Haematobium
    - 600 million worldwide exposure
    - Associated with development of muscle invasive TCC
    - Increased risk of SCC AND TCC
    - 6-13 Year Latency
    - Risk increased by 5 fold
2. Aetiology

Genetics

- Tumours arise out of aberration in normal regulation:
  - Cell differentiation
  - Proliferation
  - Apoptosis

1. Slow Acetylators of 4-Aminobiphenyl

- Acetylation capacity determined by NAT1 / NAT2 genes on Chromosome 8
- Via N-Acetyltransferase & Glutathione S-Transferase
- Induction of cytochrome p450 demethylating enzyme
- Smokers lacking gene x1.8 risk/ nonsmokers no increased risk

2. Tumour Suppressor Gene 17p

- The TP53 gene (17p13.1) codes for a 53 kDa phosphoprotein - p53
- Exists as a multimeric form
- Loss contributes to >50% of human cancers (Hollstein 1991)
- Functions of TP53 are complex but its protein increases in activity
Visible Haematuria (VH)
- 22% harbour a urological malignancy

Non-Visible Haematuria (NVH)
- Symptomatic (s-NVH) i.e. LUTS
- Asymptomatic (a-NVH) i.e. no LUTS
- 5% Harbour a urological malignancy

- Sensitivity: Dipstick of fresh urine ≈ MSU
- Positive ≥+1 (haemolysed or non-haemolysed)
- Trace = negative
3. The Haematuria Clinic

'Significant' Haematuria

- Any single VH
- Any single s-NVH (exclude UTI/transient cause)
- Persistent a-NVH (exclude UTI/transient cause)
- 2 out of 3 dipstick positive for NVH
- Evaluate regardless of anti-coag/anti-platelet Rx
3. The Haematuria Clinic

Diagnosis

Baseline:
- FBC, Renal function, Glucose, Clotting
- PSA, CA-125

Urinary:
- MSU
- Cytology

Upper tract imaging:
- Renal USS
- CT Urography

Flexible Cystoscopy:
- White Light vs Blue Light (NBI)
3. The Haematuria Clinic

Upper Tract Imaging

Incidence of pathology:
- Upper tract UCC 1.5/100,000
- Renal cancer 10/100,000
- Sensitivity of modality
- Upper tract lesions lower limit of detection:
  - IVU 3cm, U/S 2cm, CT 1cm
- Bladder:
  - Cystoscopy is “Gold Standard”

- Prospective Study
- 1930 Haematuria patients (982 micro)
- 14 UT tumours
- 4 UT tumours missed by IVU or U/S alone
3. The Haematuria Clinic

Urine Cytology

- Malignant cells – Specificity 95% & Sensitivity 30-50% with G3 95% sensitivity
- Suspicious cells – Specificity 70% & Sensitivity 70%
- Subjective assessment
- Gregoire J Urol (1997)157;1660
3. The Haematuria Clinic

White Light FC

- 3.4-20.6% missed ‘recurrences’ with single index tumour
- 7.4-45.6% missed ‘recurrences’ with multiple index tumours
- 32-36% recurrence at 8 weeks redo TURBT
- 70% recurrence for high grade tumours
- 38.1% of CIS lesions detected
- 71.4% of patients with CIS detected by white-light

3. The Haematuria Clinic

Blue Light / NBI

- **5-ALA**
  - Pre-treat for 3 hours
  - Cystoscopy with krypton ion laser
  - 20-90% increase in detection rates, similar specificity

- **HAL (Hexvix)**
  - Lipophilic hexyl ester
  - 2x fluorescence, 1 hour pre-treatment
  - 20% mean increase in sensitivity, especially for CIS

- **Hypericin (St John’s wort)**
  - Red fluorescence
  - CIS detection Sensitivity = 93%, specificity = 98.5%
4. Pathology

Grading

WHO
1973 - Benign papilloma + G1 G2 and G3 carcinomas

2003 - Cytological and architectural criteria
1. Papilloma
   Small, normal urothelium
2. PUNLMP
   Cytologically normal but thickened epithelium
3. Low grade urothelial cancer (LGUC)
   Degree of cytological atypia
   Progression rates 10% and 13% at 45 and 90 months
4. High grade urothelial cancer (HGUC)
   Progression rates 23% and 51% at 45 and 90 months
CIS - Any UCs in non pap uro lining, NOT full thickness
4. Pathology

**Staging**

- TNM system
- Based on tumour invasion through Bladder Wall, Visceral and Nodal Metastases
- Applicable to TCC and SCC
5. TURBT

EORTC Data

- 2410 Patients, recurrence rates 7-45%
- Superficial disease
- 2nd TURBT within 2-6 weeks
  - 15% had persistent T1
  - 31% had non viable tumour
  - 49% no muscle submitted
- If 2nd TUR has Lamina Propria, then cystectomy upstaging negligible

T1 disease

- 15-53% residual invasive tumour
- 4-29% upstaged to muscle invasive
5. TURBT

Complications

- 5% overall
- 2-3% bleeding
- 1-3% perforation
- Manage conservatively
- 58% silent perforation
- No extravesical tumour at 2 years
- MIBC TUR
- No upstaging (+ve nodes at cystectomy)
- No significant dissemination

Desgrandchamps Br J Cancer (1999)81:832-4
5. TURBT

Re-Resection

**Indication:**
- High risk disease
- Incomplete resection
- No muscle in initial specimen
- Improve staging accuracy + NMIBC treatment

- Reduced 3 year RR Recurrence by 42-58%
- Increased BCG response 24-35%
- MMC not compensate for inadequate TUR
- Progression risk 352 patients with T1 disease
  - Residual T1 at 2nd TUR → 76% progress to MIBC
  - No residual T1 at 2nd TUR → 14% progress to MIBC

Herr BJU Int (2006) 97:1194-8
6. Radical Cystectomy

• **Radical Cytsectomy**
  - Includes formation of Ileal Conduit Urinary Diversion with Pelvic Lymphadenectomy

• **Complications:**
  - Reoperation, Ileus, Stomal Hernia, Uretero-Ileal Anastamotic Stenosis, DVT, PE, Chest Infection, MI, CVA, Death

• **Indication**
  - Organ Confined T2+ Disease
  - Recurrent CiS or G3 disease despite BCG
  - pTa disease difficult to manage endoscopically
  - Prostatic Urethral Disease

• **Prognosis**
  - 5 year survival if untreated <5%
  - 5 year survival for T1 & Cis disease = 90% +
  - 5 year survival for T2 & T3a disease = 60%
  - 5 year survival for T3b disease = 35%
  - 5 year survival for T4a disease = 10-25%
7. Radical Radiotherapy

- **Radical Radiotherapy**
  - Total Dose 66Gy in 30 fractions over 6 weeks
  - Local Recurrence in 30%
  - Increasing role for Neoadjuvant Chemotherapy

- **Complications:**
  - Radiation Cystitis, Proctitis, VH, Storage LUTS

- **Indication**
  - Organ Confined T2+ Disease

- **Prognosis**
  - 5 year survival T1 & T2 disease = 40%
  - 5 year survival for T3a disease = 35%
  - 5 year survival for Salvage Cystectomy 30-50%