

# 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

# 3.The Haematuria Clinic

## BAUS & Renal Association 2008

### 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  $\approx$  MSU
- Positive  $\geq +1$  (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”

### Khadra et al J.Urol (2000)

- 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**

**Brausi Eur Urol (2002)41:523-31**

**Jakse Eur Urol (2004)45:539-46**

**Jocham J Urol (2005)174:862-6**

# 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

Eble WHO classn. (2004)

# 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
- 2<sup>nd</sup> 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
- Brausi Eur Urol (2002)41:523-531



# 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

Balbay J Urol (2005)174:2262-3

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 J Urol (2005)174:2134-7

Herr BJU Int (2006)97:1194-8

Zurkirchen Urol Int (2004)72:99-102

# 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%