Bladder cancer

**Demographics**
Common
~65,000 cases per yr in US
10,000 per year in UK
4th most common cancer in men; 9th in women
Rising in men despite falling smoking rates in men cf. women ? why
Incidence increases with age
Male:Female 3:1
Whites > blacks > hispanics
Industrialised World – Heavy Industry/Smoking
Schistosomiasis endemic areas
Very rarely found at post-mortem - almost always presents in vivo

**Aetiology**
Cigarette smoking
  RR x4
  Never return to baseline – 40% reduced risk after 4 yrs
  Culprit never identified (? 4-aminobiphenyl – broken down by
  N-acetyltransferase 2, which is polymorphic. Slow NAT2 acetylators a/w
  ~ 40% increased risk of bladder cancer)
Occupational exposure (aromatic amines, aniline dyes, aldehydes)
  Tanner, rubber industry, painter, autoworker, dye-worker, dry-cleaner, hairdresser
Phenacetin analgaesia
  Similar chemical structure to aniline dyes
  High volume usage a/w increased risk
  Upper urinary tract and lower tract cancers (lower tract later)
  No association with other analgaesics
Chronic cystitis/infection
  A/w increased risk of squamous cancer
  10% of indwelling catheters at 10 years (50% invasive at diagnosis)
Chronic schistosomiasis a/w SCC (?parasitic conversion of urea to nitrites)
Chronic HPV may play a role in the immunocompromised
Pelvic irradiation
  Typically female
  2-4 fold increased risk
Cycophosphamide therapy
  9-fold increased risk
  Tumours occur 6-13 yrs after cyclophosphamide
  Thought to be due to metabolite acrolein
  Reduced risk with uroprotectant mesna (2-mercaptoethanesulfonic acid)
Arsenic ingestion
  Blackfoot disease in Taiwan
Aristolochia fangchi
Chinese herb used for weight reduction
Import into Belgium a/w high number of bladder cancers

Family history
- Probably unlikely
- Slightly increased risk in relatives of index cases, but risk higher in 2nd and 3rd degree relatives cf. 1st degree (Klemeney 1997)

NB. When smoking controlled for, no evidence that coffee or tea-drinking a/w increased risk of bladder cancer. Artificial sweeteners cause bladder cancer in rats but non-physiological amounts and no evidence in humans from case-control studies.

Presentation

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Painless haematuria</td>
<td>Very common</td>
</tr>
<tr>
<td>85% of patients (however in patients with a cystoscopically detectable lesion, haematuria is almost always found if enough specimens are taken)</td>
<td></td>
</tr>
<tr>
<td>Irritative LUTS</td>
<td>Occasional</td>
</tr>
<tr>
<td>Flank pain</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Lower limb oedema</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Pelvic mass</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Rare</td>
</tr>
<tr>
<td>Bone pain</td>
<td>Rare</td>
</tr>
</tbody>
</table>

At presentation

- 75-80% Superficial
  - 70% Ta
  - 20% T1
  - 10% CIS

(20-30% of these tumours will become MI on f/up)

- 25-30% Muscle-invasive (~50% will have occult mets)

Overall

- 55-60% low-grade
- 40-45% high-grade lesions (~ half MIBC)

Pathology

Transitional cell carcinoma

Microscopic features cf. normal epithelium:

- increased number of epithelial cell layers
- papillary foldings of the mucosa
- loss of cell polarity
- abnormal cell maturation from basal to superficial layers
- increased nuclear-cytoplasmic ratio
prominent nucleoli
clumping of chromatin
increased number of mitoses (Koss, 1975).
Growth may be papillary, sessile, nodular, infiltrating, flat intraepithelial or mixed

There are now molecular and cytogenetic data to support the well-established clinical impression that low-grade (all well-differentiated and most moderately differentiated) tumors and high-grade (poorly differentiated) tumors have fundamentally different origins, with the former losing one or more suppressor genes on chromosome 9q and the latter having TP53, RB, and/or P16 abnormalities as early events. 1973 WHO grading system changed to reflect this.

<table>
<thead>
<tr>
<th>Table 2: WHO grading in 1973 and in 2004 (7,8)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1973 WHO grading</strong></td>
</tr>
<tr>
<td>Urothelial papilloma</td>
</tr>
<tr>
<td>Grade 1: well differentiated</td>
</tr>
<tr>
<td>Grade 2: moderately differentiated</td>
</tr>
<tr>
<td>Grade 3: poorly differentiated</td>
</tr>
<tr>
<td><strong>2004 WHO grading</strong></td>
</tr>
<tr>
<td>Urothelial papillomas</td>
</tr>
<tr>
<td>Papillary urothelial neoplasm of low malignant potential (PUNLMP)</td>
</tr>
<tr>
<td>Low-grade papillary urothelial carcinoma</td>
</tr>
<tr>
<td>High-grade papillary urothelial carcinoma</td>
</tr>
</tbody>
</table>

**Papilloma** papillary lesion with a fine fibrovascular core covered by normal bladder mucosa. Normal layers and no cytological abnormalities. Extremely rare. If solitary and no co-existent TCC can be considered benign.

**PUNLMP** Old grade 1 thin fibrovascular stalk with a thickened urothelium containing more than seven cell layers slight anaplasia and pleomorphism with rare mitotic figures. often recur, and recurrences may be of higher histologic grade and stage

**LGPUC** Old grade 2 Wider fibrovascular core, greater disturbance of the base-to-surface cellular maturation, and a loss of cell polarity. The nuclear-cytoplasmic ratio is higher, with more nuclear pleomorphism and prominent nucleoli. Mitotic figures are more frequent. May be difficult to differentiate between PUNLMP and LGPUC in new classification

**HGPUC** Old grade 3 No differentiation from basement membrane to the surface. Marked nuclear pleomorphism with high nuclear-cytoplasmic ratio and mitoses.
Molecular Pathology
Inactivation/mutation of tumour suppressor genes common
  p53 (TP53 gene locus on short arm of chromosome 17)
    Mutated forms accumulate in cells but inactive
    Impaired DNA repair and angiogenesis inhibition (failed production
    of thrombospondin - p53 dependent potent angiogenesis inhibitor)
    Single mutated form dimerises with wild-type p53, inactivating it.
    Therefore gene therapy by TP53 replacement unlikely to work
  Rb (RB gene on chromosome 13q)
  p16 (short arm of chromosome 9)
  p21
    Rb puts a brake on E2F, a cyclin responsible for G1S transition
    Mutated Rb product therefore favours increased cell cycling. p16 and
    p21 prevent cyclin D1 mediated inhibition of Rb
Oncogene activation less commonly seen
  RAS signal transduction molecule most common
Upregulation/overexpression of normal cell signalling molecules
  EGFR overamplication a/w aggression
  E-cadherin downregulation a/w invasion

Chromosome 9 loss (especially 9q) early events in low-grade superficial
cancer (often FGFR3 mutations)
p53 mutation and RB loss associated with high-grade aggressive cancers
NB. Mutations of p53 and FGFR3 mutually exclusive

B.

![Image](image-url)  
**Fig. 1.2 Regulation of cell-cycle G1/S checkpoint**

A. Schematic representation of the eukaryotic cell cycle. During G1, cells increase in size, produce RNA and synthesise proteins in readiness for DNA synthesis. The G1/S checkpoint represents an important regulatory mechanism ensuring defective cells cannot proceed to S phase. B. Schematic highlighting the contribution of some molecular targets to the G1/S checkpoint. Arrowheads represent stimulatory effects; blocked lines represent inhibitory effects. Rb exerts inhibitory effects on E2F1, which is responsible for G1 to S transition. p53 dependent products, including p21**^{WAF1/CIP1}** also inhibit G1 to S transition via cyclin D1 and cyclin E (not shown).

**Spread**

Two theories postulated concerning development and recurrence of bladder cancer (jury still out):

- **Field change (polychronotopicity)**
  - Suggested by multiple tumours at different sites, often separated by long periods of time

- **Clonal seeding of primary tumour**
  - Some evidence from molecular studies (LOH assay). However studies usually performed on high grade disease (and even in these studies some evidence of polyclonality)

<table>
<thead>
<tr>
<th>Spread</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct extension</td>
<td>High MMP-2:TIMP ratio</td>
</tr>
<tr>
<td></td>
<td>Reduced E-cadherin a/w reduced survival</td>
</tr>
<tr>
<td></td>
<td>High urokinase plasminogen activator</td>
</tr>
<tr>
<td></td>
<td>Extension growth direct (60%), tenticular (25%) or superficial spreading (10%)</td>
</tr>
<tr>
<td></td>
<td>Direct extension closely related to risk of mets</td>
</tr>
<tr>
<td></td>
<td>Prostate extension seen in 40% of cases at cystoprostatectomy (40% have stromal invasion – not truly T4 disease – survival equivalent to T2 disease)</td>
</tr>
</tbody>
</table>

| Implantation    | Important means of spread for TCC                                       |
|                 | Denuded urothelium commonest site of implantation (bladder, prostate or urethra) |
Occasionally abdominal wounds or retroperitoneum (post-perforation)
Provides rationale for immediate post-operative chemotherapy

Lymphatic spread
May occur independently of haematogenous mets
Up to one third of pts dying with bladder cancer have no LN mets at post-mortem
Pelvic nodes commonly involved
- Obturator nodes 74%
- External iliac nodes 65%
- Pre-sacral nodes 20%
- Paravesical nodes 16%
- Common iliac nodes 20% (always with above)

Haematogenous
- Liver 38%
- Lung 36%
- Bone 27% (esp bilharzial cancer)
- Adrenals 21%

Staging

Table 1: 2002 TNM classification of urinary bladder cancer

<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>T2a</td>
</tr>
<tr>
<td>T2b</td>
</tr>
<tr>
<td>T3</td>
</tr>
<tr>
<td>T3a</td>
</tr>
<tr>
<td>T3b</td>
</tr>
<tr>
<td>T4</td>
</tr>
<tr>
<td>T4a</td>
</tr>
<tr>
<td>T4b</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N - 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>MX</td>
</tr>
<tr>
<td>M0</td>
</tr>
<tr>
<td>M1</td>
</tr>
</tbody>
</table>
EUA and Primary TUR
Superficial bladder cancer a/w extremely low risk of metastasis (Freeman 1995). Therefore first Rx decision based wholly on whether the patient has a superficial or muscle invasive tumour
Emphasises need for careful TUR including sampling of muscle layer within bladder. EUA advocates separate biopsies of the tumour base and separate ‘near biopsies’ of larger tumours to exclude CIS
Bimanual examination may be useful for determining deep muscle/perivesical penetration from superficial disease but is most useful to assess for tumour fixation in the presence of a MIBC.
Random biopsies not recommended unless positive cytology and a non-visible tumour because biopsy denudes epithelium and encourages tumour implantation. Yield approximately 2%.
TUR biopsies of prostate recommended in those considered fit for surgery with obvious solid tumours to guide need for urethrectomy.

Role of re-resection
A large proportion of patients develop a recurrence at the site of the initial TUR, presumably due to inadequate resection or re-implantation.
Risk characterised in a number of studies with differing outcomes:
  1. Brausi 2002: 2,410 pts from 7 EORTC trials – 13.1% overall
  2. Herr 1999: Up to 75% of patients with non-invasive (Ta, Tis,T1) disease had residual disease at re-resection performed at 2-6 weeks (Herr 1999). Of these 25% = T0; 31% = Ta; 24% = T1 and 20% muscle invasive (T2).
Of the 20% patients with muscle-invasive disease at re-resection, 84% had T1 tumours at primary TUR – forms basis for recommendation of re-resection in T1 disease [interestingly 11/16 of these were tumours in which no muscle was resected at primary TUR (40% of all T1 disease)]
Herr 2006 showed that presence of T1 disease at re-resection a/w disease progression in 76% patients despite BCG (progression rates for TaG3 and CIS 16% and 23% respectively). Risk factors for progression on multivariate analysis were: (i) residual disease on re-resection; (ii) persistence of tumour at first post-BCG cystoscopy NB.

Is re-resection itself therapeutic?
Grimm 2003 Observational study of patients undergoing re-resection vs. primary TUR alone. R1 in 33% pts (over half in patients with T1 disease). 3yr recurrence rate 32% vs. 61% respectively

Radiological staging

CT Local T staging, pelvic and para-aortic LN and visceral mets
Ideally performed prior to TURBT
Contrast improves staging
Can only detect gross extravesical extension, lymph nodes 1-2cm and liver mets >1cm
Most non-calcified nodules >= 1cm on CT are metastases
Misses positive lymph nodes in 40-70% patients (Paik 2000)

MRI
Slightly better than CT for local T-staging and LN mets but local understaging estimated in 30-50%
Sn/Sp can be improved for LN staging by using ferromagnetic particles or Gd-DTPA (Baretsz – 75% sensitivity and 96% specificity LN mets) – remains largely experimental at present
More sensitive than CT for detection of bone metastases

Bone scan
Seldom positive in the presence of normal alkaline phosphatise – may be omitted if LFTs normal

Role of lymphadenectomy
Standard lymphadenectomy
  Slightly above iliac bifurcation to femoral canal
  From genitofemoral nerve to bladder pedicle
Limited evidence that a small number of patients with micrometastases may be cured by LND
Number of lymph nodes sampled a/w improved survival post cystectomy, regardless of whether positive or not (see radical cystectomy section)

Experimental modalities
Transvesical USS staging – single report in nineties of 100% sensitivity and 98% specificity for distinguishing muscle-invasive from superficial disease (as compared with TUR specimens or radical cystectomy specimens) Not been repeated
Molecular staging – a number of studies have shown promise, including one study of patients with negative nodes at cystectomy, showing that PCR positivity for uroplakin 2 a/w relapse in 70% vs. relapse in 5% for PCR-negativity.

Prognosis

Prognostic factors for recurrence and progression (6)
  Stage
  Grade
  Presence of CIS
  Multifocality
  Size
  Prior recurrence rate
  ? Micropapillary variant
Parmar criteria (prognostic factors for recurrence) (Parmar & Friedman 1989)

Only 2 criteria: number of tumours at diagnosis and recurrence at 3 mo.
Divided into 3 prognostic groups:

- Parmar low risk: Solitary, no recurrence ~25% rec @ 3yrs
- Parmar int risk: Multiple, no recurrence ~55% rec @ 3yrs
- Parmar high risk: Multiple, recurrence ~85% rec @ 3yrs

EORTC

Problem with Parmar above is that it does not differentiate between the risk of recurrence and the risk of progression. Thus, the EORTC risk tables were devised using data from 2596 patients from seven EORTC trials [NB. 78% pts received intravesical chemotherapy. No patient received repeat TUR or BCG therapy]

<table>
<thead>
<tr>
<th>Factor</th>
<th>Recurrence</th>
<th>Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of tumours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2–7</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>≥8</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Tumour diameter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 3 cm</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>≥3 cm</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Prior recurrence rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary tumour</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>≤1 recurrence/year</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>&gt;1 recurrence/year</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Category</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ta</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>T1</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>CIS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Yes</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>G2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>G3</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Total score</td>
<td>0–17</td>
<td>0–23</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recurrence score</th>
<th>Probability of recurrence at 1 yr (95% CI)</th>
<th>Probability of recurrence at 5 yr (95% CI)</th>
<th>Recurrence risk group</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>15% (10–19%)</td>
<td>31% (24–37%)</td>
<td>Low risk</td>
</tr>
<tr>
<td>1–4</td>
<td>24% (21–26%)</td>
<td>46% (42–49%)</td>
<td>Intermediate risk</td>
</tr>
<tr>
<td>5–9</td>
<td>38% (35–41%)</td>
<td>62% (58–65%)</td>
<td>Intermediate risk</td>
</tr>
<tr>
<td>10–17</td>
<td>61% (55–67%)</td>
<td>78% (73–84%)</td>
<td>High risk</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Progression score</th>
<th>Probability of progression at 1 yr (95% CI)</th>
<th>Probability of progression at 5 yr (95% CI)</th>
<th>Progression risk group</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.2% (0–0.7%)</td>
<td>0.8% (0–1.7%)</td>
<td>Low risk</td>
</tr>
<tr>
<td>2–6</td>
<td>1% (0.4–1.6%)</td>
<td>6% (5–8%)</td>
<td>Intermediate risk</td>
</tr>
<tr>
<td>7–13</td>
<td>5% (4–7%)</td>
<td>17% (14–20%)</td>
<td>High risk</td>
</tr>
<tr>
<td>14–23</td>
<td>17% (10–24%)</td>
<td>45% (35–55%)</td>
<td>High risk</td>
</tr>
</tbody>
</table>

CI = confidence interval.


Bladder cancer
Overall factors predicting:
- Recurrence: multiplicity, size and a positive three-month cystoscopy.
- Progression: grade, stage, recurrence, CIS and size
- Cancer death: grade and recurrence rate

**Diagnosis**

Standard methods of diagnosis

<table>
<thead>
<tr>
<th>Method</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>False negatives arise as haematuria intermittent in 25%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dipstick haematuria</td>
<td>40 – 92%</td>
<td>51 – 96%</td>
<td></td>
</tr>
<tr>
<td>Cytology</td>
<td>28 – 76%</td>
<td>81-100%</td>
<td>At best, still misses ~20% high grade lesions</td>
</tr>
<tr>
<td>Cystoscopy</td>
<td>Reference standard for studies of markers</td>
<td>Surprisingly high false negative rates reported (10-40%)</td>
<td>Specificity fairly low ~ 40%</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>61.96% (17%-77.5%)</td>
<td>72.4% (46%-92%)</td>
<td></td>
</tr>
<tr>
<td>Specificity</td>
<td>72.4% (46%-92%)</td>
<td>75.5% (50.5%-95%)</td>
<td></td>
</tr>
<tr>
<td>False negatives</td>
<td>95.72% (81%-100%)</td>
<td>87.15% (69%-99%)</td>
<td></td>
</tr>
</tbody>
</table>

Due to limitations of cytology, search for molecular markers continues:

- For screening Reference standard haematuria
  - High sensitivity
  - High positive predictive value
- For surveillance Reference standard cytology (high-grade) or cystoscopy (low-grade)
  - High specificity
  - High negative predictive value

**Molecular markers (Konet 2006)**

<table>
<thead>
<tr>
<th>Bladder cancer marker [references]</th>
<th>Mean sensitivity (range)</th>
<th>Mean specificity (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytology [1,9,10,13,7,50–46]</td>
<td>48.00% (28%-74.47%)</td>
<td>95.72% (81%-100%)</td>
</tr>
<tr>
<td>NMP22 [1,10,20,24,26,38,32,40–55]</td>
<td>67.49% (31%-91.7%)</td>
<td>74.38% (51.9%-94.3%)</td>
</tr>
<tr>
<td>BTA stat [6,8,30,3,36,40,56–65]</td>
<td>61.71% (32.8%-39%)</td>
<td>73.67% (54%-95%)</td>
</tr>
<tr>
<td>BTA TRAK [5,25,33,40,59,64–66]</td>
<td>61.96% (17%-77.5%)</td>
<td>75.5% (50.5%-95%)</td>
</tr>
<tr>
<td>Tetranucleotides [4,6,9,13,67–71]</td>
<td>72.4% (46%-92%)</td>
<td>87.15% (69%-99%)</td>
</tr>
<tr>
<td>Hyaluronic acid and hyaluronidase [62,72,73]</td>
<td>94% (91.9%-100%)</td>
<td>80.93% (70%-88.8%)</td>
</tr>
<tr>
<td>Flow cytometry and Quanticell assay [28,30,35,37,74]</td>
<td>51.08% (45%-72%)</td>
<td>80.62% (70.6%-95%)</td>
</tr>
<tr>
<td>Fluorescence in situ hybridization [6,57,75]</td>
<td>77% (73%-83%)</td>
<td>96% (95%-100%)</td>
</tr>
<tr>
<td>ImmunoCyte [39,75–77]</td>
<td>55.2% (35.5%-86.1%)</td>
<td>78.7% (73%-83.9%)</td>
</tr>
<tr>
<td>Cytokeratin 29 [38,78–82]</td>
<td>82.8% (71%-94.5%)</td>
<td>73.37% (36%-96.7%)</td>
</tr>
<tr>
<td>Cytokeratin 8 and 18 (UBC) [33,51–53,63]</td>
<td>60.7% (48.7%-70%)</td>
<td>83.82% (79%-95%)</td>
</tr>
<tr>
<td>LeuN X antibody [54,61]</td>
<td>87.1% (79.8%-94.1%)</td>
<td>61.65% (36.9%-86.4%)</td>
</tr>
<tr>
<td>Hemoglobin dipstick [4–7]</td>
<td>71.2% (47%-90.5%)</td>
<td>67.27% (54%-84%)</td>
</tr>
<tr>
<td>CYFRA 21.1 [51,84]</td>
<td>74.15% (69%-79.3%)</td>
<td>91.3% (88.6%-94%)</td>
</tr>
<tr>
<td>Survivin [85]</td>
<td>64%</td>
<td>93%</td>
</tr>
</tbody>
</table>

Screening:

No single test considered effective for screening for bladder cancer
Repetitive haematuria testing has been shown in non-randomised setting to be associated with improved survival cf. observational non-screened group. (Messing 1992; Britton 1989 (Leeds, UK)). A number of markers have high sensitivities (hyaluronidase/hyaluronic acid, BLCA4, microsatellite repeats, telomerase) yet have not supplanted haematuria for screening as yet. Only exception is study of Hemstreet (1999,2001) which correlated risk according to a panel of urine biomarkers (DNA, Gactin:Factin, M344) is a group of high-risk (benzidine) exposed Chinese workers. Positivity stratified patients into risk groups; a positive biomarker occurred 15-33 months before bladder cancer was diagnosed (more biomarkers – shorter time to cancer).

Surveillance:

From above, none of the markers have a specificity better than cytology for high-grade disease; therefore it is difficult to see how they could supplant cytology in the surveillance of high-grade disease. For lower grade disease, many of the markers have better sensitivities than cytology, but false negative rates remain too high to completely obviate the need for cystoscopy. Potentially a number of markers may find a role in reducing the frequency of cystoscopy rather than supplanting it.

Photodynamic diagnosis

Abnormal levels of HEME intermediate protoporphyrin 9 accumulate in bladder cancer cells; mechanism unknown – possibly defective ferrochelatase or intracellular iron deficiency. Protoporphyrin 9 + blue light (400 nm, very strong)) = red fluorescence (640nm – very weak). Yellow filter and slow shutter speed results in absorption of almost all blue light and amplification of red light. Utility of PDD diagnosis (Jocham review 2008)

1. Improved detection of bladder cancer
Bladder cancer

Overall sensitivity 93% vs. 73%
Difference largely attributable to CIS
Very high sensitivity 97% for residual disease after BCG

2. Reduces residual tumour rates
   3 of 4 randomised studies
   Residual tumour rate 38%-82% less in PDD arm
   Largest (Alken 2007) showed no difference, but only published in abstract form EAU 2007

3. Reduces recurrence rates
   Two long term studies have shown that PDD improves recurrence-free survival rates

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of patients available for efficacy analysis</th>
<th>Recurrence-free survival rate, %</th>
<th>Median follow-up, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denkichenko [99]</td>
<td>102</td>
<td>41</td>
<td>42</td>
</tr>
<tr>
<td>Denzinger [10]</td>
<td>191</td>
<td>71</td>
<td>86</td>
</tr>
</tbody>
</table>

PDD = following photodynamic diagnosis; WLC = following white light cystoscopy.

4. Cost effective

Problems
   - Poor specificity (high false positives)
   - Inflammation
   - Recent intravesical therapy
   - Acute viewing angle (BN and diverticulae)
   - Requirement for adequate pre-op instillation
   - No effect on progression rates or disease-specific survival

Side effects
   - Very well tolerated generally
   - Irritative LUTS
   - Systemic absorption very low
Superficial bladder cancer

Overall 70-88% of Ta and T1 tumours recur after endoscopic treatment
Risk of recurrence related to:
- No. of tumours at initial diagnosis
- Recurrence rate
- Size of tumour
- Grade
- **NOT** Stage

Progression related closely to grade **AND** stage. High grade disease much more likely to progress to invasive disease
- Ta, T1G1, T1G2 5-8% progression
- T1G3 50% progression

Risk Stratification (slightly different for EAU, AUA and NCCN and BAUS Oncology)

<table>
<thead>
<tr>
<th>EAU [1]</th>
<th>G1-2Ta Low risk of tumour recurrence and progression (EORTC recurrence score = 0; progression score = 0)</th>
<th>Multifocal G2Ta, G1G1, solitary G1G1</th>
<th>Multifocal G2Ta, G3Ta-T2a, CIS High risk of progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC [9-13] Low-grade Ta</td>
<td>Low-grade Ta with high risk factors for recurrence or recurrent low-grade Ta tumours</td>
<td>Intermediate or high risk of recurrence and intermediate risk of progression (EORTC recurrence scores ranging from 1-9, progression scores ranging from 1-6)</td>
<td>(EORTC progression scores ranging from 7-23)</td>
</tr>
<tr>
<td>NCCN [8] G1-2Ta</td>
<td>G1-2Ta, solitary G1-2Ta</td>
<td>Multifocal G1-2Ta, G3Ta, CIS (CIS listed separately)</td>
<td>High-grade Ta, all T1, CIS</td>
</tr>
<tr>
<td>AUA [45] Small volume, low-grade Ta</td>
<td>Multifocal and/or large volume low-grade Ta</td>
<td>High grade Ta, all T1, CIS</td>
<td></td>
</tr>
</tbody>
</table>

CIS = carcinoma in situ, EORTC = European Organization for the Research and Treatment of Cancer.

BAUS Section of Oncology

International Bladder Cancer Group has tried to simplify stratification:

- **Low risk**  Solitary Ta G1/2
- **Int. risk** Multiple or recurrent G1/2 tumours
- **High risk** Any T1, G3 or CIS
Primary Tumour characteristics | Risk of recurrence | Risk of progression
--- | --- | ---
Solitary pTa G1 | 15% at 1 yr, 31% at 5 yrs | 0.2% at 1 yr, 0.8% at 5 yrs
Solitary pTa G2 | 24% at 1 yr, 46% at 5 yrs | 0.2% at 1 yr, 0.8% at 5 yrs
Multifocal pTa G1 | 24% at 1 yr, 46% at 5 yrs | 1% at 1 yr, 6% at 5 yrs
Multifocal pTa G2 | 24% at 1 yr, 46% at 5 yrs | 1% at 1 yr, 6% at 5 yrs
Solitary pTa G3 | 24% at 1 yr, 46% at 5 yrs | 1% at 1 yr, 6% at 5 yrs
Solitary pT1 G2 | 24% at 1 yr, 46% at 5 yrs | 1% at 1 yr, 6% at 5 yrs
Multifocal pTa G3 | 38% at 1 yr, 62% at 5 yrs | 5% at 1 yr, 17% at 5 yrs
Multifocal pT1 G2 | 38% at 1 yr, 62% at 5 yrs | 5% at 1 yr, 17% at 5 yrs
pT1 G3 no CIS | 24% at 1 yr, 46% at 5 yrs | 5% at 1 yr, 17% at 5 yrs
pT1 G3 with CIS | 24% at 1 yr, 46% at 5 yrs | 17% at 1 yr, 45% at 5 yrs
CIS alone* | |*

NB. Using EORTC risk tables * not assessed – tables just for Ta T1 tumours

Management of low-risk superficial disease

Immediate single instillation of adjuvant intravesical chemotherapy

Strong 1a evidence

**Sylvester Meta-analysis (2004) (n=1476)**

Studies including Oosterlink EORTC (1993) and Tolley MRC trial (1996) using MMC, epirubicin, thiotepa and doxorubicin

84% had solitary tumours, 16% had multiple.

68% Ta, 32% T1, 10% G3.

At median follow-up of 3.5 years, 36.7% of patients receiving a single dose of adjuvant chemotherapy had a recurrence cf. 48.4% without. **Overall, 12% absolute risk reduction and 39% relative risk reduction in favour of immediate instillation of chemotherapy.**

Similar effect was seen for solitary or multiple tumours. For multiple tumours the risk fell from 82% to 65%, but remained high, indicating that further treatment is required for this subset of patients.

Cost benefit analysis suggests that 9 patients require treatment to prevent one recurrence

Similar efficacy for MMC, epirubicin, doxorubicin. Thiotepa ineffective according to dose

Timing of post-operative instillation is crucial

- The Finnbladder group have shown that by delaying instillation overnight the risk of recurrence is increased twofold (Kaasinen 2002).
- Results corroborated by Bouffioux (1995) iss a cohort going on to receive maintenance chemotherapy
- Generally recommended that instillation should occur within 6 hours of surgery.

Immediate post-operative instillation is contraindicated in patients with suspected or overt bladder perforation (Oddens 2004)
Management of intermediate-risk superficial disease

Additional intravesical chemotherapy for intermediate risk bladder cancer
Intermediate risk tumours have a overall risk of recurrence of 45% and a progression rate of 1.8% (Millan-Rodriguez 2000).
Evidence for adjuvant vs. single chemotherapy:
1. Prophylactic effect of single immediate instillation of intravesical chemotherapy only lasts approximately 500 days (Hinotsu 1999)
2. Significant risk reduction with adjuvant vs. single Rx
   (i) Lamm (1995) concluded that overall benefit from pooled data approximately 14% risk reduction. Results relatively short-term.
   (ii) Pawinski (1996) performed a meta-analysis of MRC and EORTC trials, concluding that adjuvant chemotherapy significantly increases recurrence-free survival compared with no adjuvant treatment. At follow-up of 7.8 yrs, recurrence rate fell from 53% to 47%, corresponding to a 6% absolute risk reduction and 11% relative risk reduction in favour of multiple adjuvant instillations
   (iii) Koga (2004) 1 yr epirubicin Rx more effective in reducing recurrence (14.8% at 3yr) vs. 3 months (36.1% at 3 yrs)

Evidence not entirely conclusive however. For example Bouffioux 1995 showed that one yr of monthly instillation no more effective than 6 months, provided 1st instillation immediately after TUR. Tolley also showed that one instillation of MMC no more effective than 5.
In general at least one year of intravesical chemotherapy advocated for intermediate therapy disease. NB. MMC after every recurrence vs. ongoing maintenance worthy of investigation.
BCG considered more efficacious cf. cytotoxics in reducing recurrence rates.
Pooled studies quote overall reduction in recurrence at ~40% and ~15% for BCG and cytotoxics respectively. (Bohle 2003). However toxicity significant.
Electromotive MMC appears to be more effective than MMC alone in reducing recurrence rates: Di Stasi (2003) (Rome; n=108) 3 groups of EMMC (6 wks 40 mg MMC and 20mA), MMC, and BCG. Response rates at 6 months were 58%, 31% and 64% respectively.

Management of high-risk superficial disease

Intravesical BCG
Recurrence
   Statistically superior to MMC in reducing recurrence in high-risk patients – 31% reduction in risk of recurrence (Shelley 2004)
Bohle et al showed a relative risk reduction of 17% in intermediate and high-risk patients for BCG vs. MMC. (absolute risk reduction of 7.8% from 38.6% to 46.4%)
Progression

Statistically significant reduction in progression vs. TUR alone

**Sylvester Meta-analysis (2002)** (n=4863)
24 trials (20 with maintenance BCG)
At median follow-up of 2.5 years, **BCG associated with absolute risk reduction of 4% (13.8% vs. 9.8%) and relative risk reduction of 27%**
Size of effect similar in papillary and CIS groups (81.6% papillary, 18.4% CIS). Only patients receiving maintenance BCG benefited. Small non-significant reductions in overall (11%) and disease-specific survival (19%) among the groups.

**Lamm (2000). SWOG 8507 trial** (n= 660). Originally not included in EORTC meta-analysis. Subsequently included at a later analysis but findings similar. Patients randomised to maintenance BCG vs. no maintenance after initial induction six week course of BCG for CIS or high risk disease. Maintenance = 3 week course of BCG at 3, 6, 12, 18, 24, 30, 26 months. Disease-free survival 76.8 months in the maintenance arm and 35.7 months in the non-maintenance arm. Overall survival 83% vs. 78% at 5 years.

Statistically superior to MMC in preventing disease progression (Bohle and Bock 2004). Maintenance required for at least a year to demonstrate superiority to MMC. No evidence for prolongation of maintenance beyond three years. Van der Meijden 2003 has shown that approximately 20% of patients will not tolerate treatment; three quarters because of local effects. The vast majority (approx 70%) stop within the first six months, with the remainder tolerating the course well.

Long-term results of BCG relatively poor. At 15 years;
- 50% progression
- 1/3 died of cancer progression
- 1/3 developed disease in upper tracts/prostate
- 27% survived with intact bladder

**BCG failure**

Definition of BCG failure unclear
Terms such as BCG-refractory, BCG resistant and BCG-relapsing proposed.

**BCG-refractory**
- Muscle-invasive disease at 3 month cystoscopy
- Persistence or recurrence of high-risk disease at 6 months (either after 6+3 or 6+6)

**BCG-resistant**
- Persistence at 3 month cystoscopy
- Low-risk or intermediate risk disease by 6 months

**BCG-relapsing**
- Recurrence after achieving disease-free state at 6 months

Patients with persistent high-grade disease at 3 months – further induction course of BCG a/w response rates of ~50% (Herr 2003)
Persistence of high-risk disease at 6 months should be considered for radical cystectomy (radical radiotherapy no place in management of high-risk superficial
Bladder cancer

Options for unfit patients:

(i) **BCG and interferon**
Small studies have shown that 1/3 dose of BCG combined with 50 mega units of interferon alpha given intravesically will produce a complete tumour response in 50% patients who have failed on BCG alone (O'Donnell, Krohn et al. 2001)

(ii) **Sequential electromotive BCG/MMC**
Combination of sequential BCG and electromotive mitomycin is associated with higher disease free survival intervals compared with BCG alone:
**Di Stasi (2006)** (n=212) reported impressive results for sequential BCG/EMMC therapy vs BCG alone in patients with T1 tumours. Regime below. Sequential treatment was associated with longer disease-free interval (69 mths vs 21 mths); lower recurrence (42% vs 58%), lower progression (9% vs. 22%), reduced overall mortality (22% vs. 32%) and reduced disease-specific mortality (6% vs 16%). Results yet to be repeated.

![Diagram of dose schedules](image)

*Figure 1: Dose schedules*

(iii) **Thermotherapy**
Theoretical advantages
- Increased permeability
- Improved DNA damage and reduced DNA repair
- Failed vasodilatation of tumour microcirculation leads to selective heating and coagulative necrosis of tumour vs. normal cells

Commonest system Synergo. Intravesical microwave application – raises temperature of bladder wall to approx. 42°C using catheter
with thermocouple feedback
Impressive efficacy reported in low-risk and high-risk tumours:
  Low-risk  17.5% vs. 57.5% recurrence at 24 months
    (Colombo 2003 – RCT)
Intermediate and high-risk disease (Van der Heijden 2004 –
non-randomised data but no progression despite 41/90 BCG
failures) Well tolerated – slightly higher bladder pain and
posterior wall burns

(iv) Photodynamic therapy (PDT)
  Similar to PDD
  Photosensitiser taken up preferentially by bladder tumour cells
  Laser light administered to bladder – liberates reactive oxygen
  species in cells containing photosensitiser
  Early studies with systemic photosensitisers a/w unacceptably high
  rates of bladder fibrosis/skin photosensitivity
  5-ALA derivatives better tolerated
  Response rates of up to 80% in patients with BCG-resistant CIS
    (Berger 2003)

(v) Radiation therapy
  Controversial
  Little evidence supporting use in high-grade superficial disease
  Older studies reported a failure of RT to prevent new tumours in the
  setting of primary disease (Goffinet 1975)
  CIS in particular appears to be a radioresistant tumour
  MRC BS06 trial 2005 – No difference for RT vs. intravesical
treatment

Carcinoma-in situ
Untreated progression rate is approximately 50% at 5 years
BCG treatment of choice. High efficacy thought to be related to high surface area
in contact with agent. Pooled data suggest initial tumour free response rate ~70%.
Drops to 50% at 4 years, and 30% at 10 years. Majority of patients recur within 5 yr
Best evidence from Sylvester meta-analysis (2005)
  9 trials comprising 700 patients comparing BCG vs. MMC
  Median follow-up 3.6 years
  Response rate (assessed at 3 or 6 months)
    68% vs. 52% in favour of BCG
  Recurrence rate
    53% vs. 74% in favour of BCG
    21% absolute risk reduction
    28% relative risk reduction
  Progression
    15% vs. 20% in favour of BCG
    5% absolute risk reduction
**26% relative risk reduction**

Persistence after one course of therapy related to high risk of progression. Herr (1989) 180 patients, Progression at 5 years = 19% in initial responders and 95% in non-responders. Second six week course can produce a response in 15-30% of patients but, increased likelihood of progression [7% actuarial risk /per course of therapy]. Failure to respond after 2 course predicates radical treatment if appropriate.
Follow-up schedules for superficial bladder cancer

5.7.1 Recommendations for follow-up cystoscopy
- Patients with low-risk (TaG1) tumours (50% of all patients) should have a cystoscopy at 3 months. If negative, the following cystoscopy is advised at 9 months and consequently yearly for 5 years.
- High-risk patients (15% of all patients) should have a cystoscopy at 3 months. If negative, the following cystoscopies should be repeated every 3 months for a period of 2 years, every 4 months in the third year, every 6 months thereafter until 5 years, and yearly thereafter. A yearly IVU should be recommended.
- Patients with intermediate-risk factors (about one-third of all patients) should have an in-between follow-up scheme, adapted according to personal and subjective factors.

Management of muscle-invasive bladder cancer

Radical treatment
No consistent evidence supporting superiority of two main radical treatments. Indeed no RCT comparing two modalities has been, or is likely to be performed.

Factors favouring surgery (9):
- Poor bladder function, especially small capacity
- Widespread CIS or CIS remote from muscle invasive tumour
- Large volume tumours
- Multifocal disease
- Pre-existing hydronephrosis
- Previous pelvic radiotherapy
- Active inflammatory bowel disease
- Bilateral total hip replacements
- Pregnancy

Factors favouring radiotherapy (2):
- Extreme old age
- Unfit for surgery

Radical radiotherapy
Indications: T2-T4b, Nx-N1, M0
Typical dose 64 Gy in 32 (2 Gy) fractions, not longer than 7 weeks.
Hypofractionation protocol 55 Gy in 20 fractions
Side-effects:
- Acute: Diarrhoea, tenesmus, proctitis, cystitis, lethargy
- Late: Impotence (30%), telangiectasia (5%), bladder shrinkage, incontinence (1%), increased bowel habit (50%), proctitis (5%), vaginal stenosis, second malignancy

Outcomes:
- Response rates 60-80%
- Local recurrence 30% at 5 yrs
- Overall survival 40-60% at 5 yrs
No RCT data comparing radical cystectomy with radical radiotherapy. Cochrane analysis (Shelley 2002) suggested improved outcomes in surgery patients, but old data, problems with comparing groups and all patients in the surgery group underwent pre-op radiotherapy. Retrospective comparative study from Leeds (Kotwal et al. 2007) showed similar treatment outcomes for patients treated with either radiotherapy or surgery despite higher age group (and presumably poorer performance status) in RT group. Local recurrence in 32% of patients in RT group, with 18% overall requiring radical cystectomy. Pooled data from Yorkshire region (Chahal 2003) showed:

**Yorkshire study**

- 398 patients in Yorkshire region 1993-96
  - 302 radiotherapy (18.8% salvage cystectomy)
  - 96 cystectomy
- 30 day/3 month mortality
  - Cystectomy 3.1%, 8.3%
  - Radiotherapy 0.3%, 1.65%
- 5 yr Survival
  - Cystectomy 36.5%
  - Radiotherapy 37.4%

Early studies showed that concurrent cisplatin chemotherapy (3 cycles of cisplatin 100mg/m² q 2wks) a/w improved pelvic control and bladder preservation rates (70% vs. 36%), with a 6% non-significant improvement in overall survival (NCI Canada Coppin 1996)

**Neo-adjuvant chemotherapy associated with an overall 5% survival benefit at 5 yrs** (ABC collaborative metaanalysis)
Radiosensitisers such as carbogen (ARCO) or carbogen nicotinamide (ARCON) promising new agents (Kaanders 2002)

**Selective bladder preservation**
Small proportion of MIBC can be treated by TURBT alone - ~10% of cystectomy specimens pT0. Approximately 33-38% rendered pT0 after neoadjuvant chemotherapy. Forms theoretical basis for selective bladder preservation. Strategies combine trimodality therapy: aggressive TURBT, neoadjuvant chemotherapy, and concurrent chemotherapy and radiotherapy (often termed chemoradiation) with mid-Rx or completion cystoscopy and re-resection to determine reponse to treatment. Responders continue Rx, whereas non-responders are offered immediate cystectomy. Good results reported from single institutions, equivalent to cystectomy (see below). No RCT data to support approach. Awaiting results of SPARE trial (see clinical trials info).
Radical cystectomy
Indications: T2-T4a, N0-Nx, M0
High-risk superficial bladder cancer
Side effects: Early
30 day mortality 1-3%
90 day mortality 2-8%
Morbidity 30%
Late
Outcomes: Local recurrence 10-12%
Disease-free survival 53% 5YS*
50% 10 YS (low risk of late recs)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>80% 10 YS (Johns Hopkins)</td>
</tr>
<tr>
<td>T2</td>
<td>70% 5YS</td>
</tr>
<tr>
<td>T3</td>
<td>35% 5YS</td>
</tr>
<tr>
<td>T4</td>
<td>25% 5YS</td>
</tr>
</tbody>
</table>

* combined – dependent on stage and LN involvement (see below from Stein 2001)

Overall survival 52% 5YS
36% 10 YS
Worse outcome if delay between detection of muscle-invasion and cystectomy >12 weeks (in chemotherapy-naive population Sanchez-Ortiz 2003)

No role for pre-operative radiotherapy (Huncharek 2008)

Similar oncological outcomes for nerve-sparing procedures. Improved continence rates also reported (Studer et al; Owen et al)

Role of LN dissection

25% of cystectomy specimens a/w positive LN
LNI directly proportional to stage (Smith 1981)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>G3pT1</td>
<td>5-10%</td>
</tr>
<tr>
<td>pT2</td>
<td>10-30%</td>
</tr>
<tr>
<td>pT3</td>
<td>30-65%</td>
</tr>
</tbody>
</table>

Capsular breach of LN mets independently a/w poor prognosis (Mills 2001)

Definitions:

- **Limited LND**: obturator packet only
- **Standard**: below common iliac bifurcation
- **Extended**: 2cm above aortic bifurcation to origin of IMA
  - Level 1 = to common iliac bifurcation
  - Level 2 = to aortic bifurcation
  - Level 3 = to origin of IMA

Multiple retrospective series reported suggesting benefit for eLND (Skinner 1982; Poulsen 1998; Leissner 2000; Mills 2001; Herr 2002) vs. standard LND

Recent evidence:

1. **Level II clearance advocated**

Abol-Enein (2004) - Extended LND in 200 patients. LN metastasis was present in 24% patients. Vast majority of LN mets to 'sentinel' obturator and internal iliac node packets, but one patient each with single met to EIA and CIA respectively. Clearance maximised by extended LND (no neoadjuvant Rx however)

Leissner (2004) – 10% of patients with single node proximal to endopelvic nodes. 7% with involvement of level 2 nodes alone.

Above papers suggest merit for eLND to aortic bifurcation. No evidence for excision of level 3 nodes at present.
2. **Number of excised LN positively correlates with survival**

Konety 2003 – SEER data comprising 1927 pts, showed a significant trend towards improved survival with more LN (irrespective of positivity) to a maximum of 14, even controlling for stage and use of chemotherapy. Interestingly, removal of more than 14 nodes was associated with a reduction in effect (see table below). Results corroborated by Stein 2003, Leissner 2000.

<table>
<thead>
<tr>
<th>No. lymph nodes (%)</th>
<th>In Situ/I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>68.6</td>
<td>60.2</td>
<td>42.7</td>
<td>32.6</td>
</tr>
<tr>
<td>1–3</td>
<td>85.7</td>
<td>70.6</td>
<td>42.9</td>
<td>59.6</td>
</tr>
<tr>
<td>4–9</td>
<td>100</td>
<td>68.2</td>
<td>46.2</td>
<td>46.2</td>
</tr>
<tr>
<td>10–14</td>
<td>100</td>
<td>85.6</td>
<td>81.5</td>
<td>49</td>
</tr>
<tr>
<td>15–19</td>
<td>100</td>
<td>75</td>
<td>64.7</td>
<td>39</td>
</tr>
<tr>
<td>20 or Greater</td>
<td>100</td>
<td>72.7</td>
<td>60</td>
<td>41.7</td>
</tr>
</tbody>
</table>

3. **No. positive nodes & LN density negatively correlates with survival.**

Stein 2003 – More than 8 positive nodes = 10% 10YDFS vs 40% for <= 8

LN Density <20% = 43% 10YDFS vs. 17% >20%

Similar results reported by Abdel-Latif 2004

**Role of urethrectomy in males**

Overall risk of urethral recurrence 8.1% (Stenzl 2002 – metaanalysis 3165 pts)

Median time to urethral recurrence 2 years

Historically, multifocality, diffuse CIS, bladder neck, and prostate involvement considered indications for urethrectomy.

Now known that multifocality and CIS not predictive (Freeman 1996); bladder neck tumour/CIS predictive of prostate involvement (Wood 1986), but recurrence

**Current risk factors:**
1. Prostate involvement (from Stein 2005)
   - Without: 5%
   - Superficial: 12%
   - Invasive*: 18%
   
   * this figure is rather low: reports vary from 18-64% for risk associated with prostatic stromal involvement. However TUR biopsy may only detect ~50% of prostate involvement

2. Positive distal urethral margin frozen section

Form of urinary diversion may have an impact on recurrence rates: Some evidence that rate of urethral recurrence lower in patients with functional vs, non-functional urethras, suggesting a possible protective effect for urine (Freeman 1999; Iselin 1997; Soloway 2004), even in the presence of prostatic stromal involvement. Emphasises importance of prostate loop biopsies in patients considered fit for surgery. However recent study of 2401 men has shown no overall survival benefit for urethrectomy (either immediate or late). Nelles 2008

Side-effects:
- Increased operative duration
- Increased local morbidity
- Increased sexual dysfunction

Role of urethrectomy in females
Urethrectomy considered a standard component of anterior exenteration. Mapping studies reveal an overall 2-12% urethral involvement by tumour at cystectomy. (DePaepe te al)

Overall urethral recurrence 3.6% (Stenzl 2002, n=841)

Bladder neck tumour involvement is most significant risk factor for urethral involvement ~50-60%

Stein et al (1998) reported the results of 71 consecutive female radical cystectomies. 5 displayed proximal urethral tumour involvement of which all had bladder neck tumours. Intraoperative frozen section of the distal urethra was seen to accurately predict final pathological classification – therefore may be a role for frozen section prior to substitution cystoplasty

Prostate-sparing cystectomy
Theoretical advantage of retained sphincter and erectile mechanisms. Typically used in concert with orthotopic bladder substitution

Different techniques
- Total prostate preservation
- Prostate capsule sparing cystectomy
  - Prior TURP
  - Synchronous Millen’s enucleation

Excellent results reported for continence (>90%) and erectile function (>80%), with equivalency to standard cystectomy in one study (Vallencien 2002). Not reproduced elsewhere as yet. Concerns over high rates of incidental prostate cancer and prostatic TCC. In one study of 235 consecutive patients undergoing
cystoprostatectomy, 48% had prostate cancer (29% Gleason 7+) and 33% had urothelial cancer.

Urinary diversion after cystectomy
4 options available for urinary diversion: ileal conduit, continent pouch, bladder reconstruction, or ureterosigmoidostomy

Continent urinary diversions require three components (Kock 1982)
  - Detubularisation of bowel to create a low-pressure, large capacity reservoir
  - An anti-reflux mechanism to protect upper tracts
  - A continence mechanism

Continence rates generally >90% daytime and >80% night-time in most continent diversions (including Studer)

Approximately 10% early complications (PE, abdominal fistula, sepsis, intestinal obstruction). Late complications up to 10% for incisional hernia, stricture (urethra, BN and ureter), and UTI. Up to 5% for bladder stones.

<table>
<thead>
<tr>
<th>Type</th>
<th>Reservoir</th>
<th>Conduit</th>
<th>Sphincter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ileal conduit</td>
<td>-</td>
<td>ileum</td>
<td>-</td>
</tr>
<tr>
<td>Mainz ureterosigmoidostomy</td>
<td>sigmoid</td>
<td>-</td>
<td>Anal</td>
</tr>
<tr>
<td>Indiana continent pouch</td>
<td>caecum</td>
<td>iliocaecal valve</td>
<td></td>
</tr>
<tr>
<td>Ileal neobladder</td>
<td>ileum</td>
<td>urethra</td>
<td>ext. urinary</td>
</tr>
</tbody>
</table>

1. Ileal conduit
   - Reliable treatment with established efficacy
   - Long-term complications common
     - Stomal complications 20%
     - Dilated renal units 30% (of these, 18% develop renal impairment, 7% dialysis dependent, and 6% die from ESRF)

2. Ureterosigmoidostomy
   - Obsolete due to high rate of ascending UTI (reflux) and increased risk of malignancy (associated with mixing of faecal and urinary streams), bowel frequency and urge incontinence
   - Recent modification (Mainz II)

3. Continent urinary diversions

4. Ileal neobladder
   - ie. Studer, Hautmann pouches
   - Hautmann pouch – increased incidence of ureteroileal stenosis cf. Studer
   - Indiana Pouch ~ 16% revision rate
   - Koch Pouch ~ 30% revision rate
   - No real evidence to support role of anti-reflux procedures

Contraindications to neobladder formation
  - Stress urinary incontinence
  - Prostate or bladder neck involvement
  - eGFR <= 35 ml/min
  - Severe intestinal disease
Unable to perform CISC
Poor mental capacity
Poor compliance
Age > 70 years

Neoadjuvant chemotherapy
Administration of systemic chemotherapy to a group of patients thought potentially curable with the intention of improving the likelihood of cure
Up to 50% of patients will have occult metastases at presentation
Theoretical advantage for neoadjuvant chemotherapy
  - Burden of disease smaller than at relapse – thus toxicity less
  - Patients generally have better performance status prior to surgery
MRC/EORTC trial of neoadjuvant cisplatin, methotrexate and vinblastine (CMV) showed 6% absolute benefit for chemotherapy at 8 yrs (43% vs. 37%) in patients receiving radical surgery or radiotherapy (Lancet 1999)
Similar benefit for 3 cycles MVAC (methotrexate, vinblastine, adriamycin and cisplatin) in SWOG study. Prolonged median survival of 77 months vs. 46 months in surgery group (Grossman 2003)
ABC metaanalysis of 11 trials (including both above) confirmed benefit, equating to an absolute survival benefit of 5% at 5 years (50% vs 45%) for platinum containing combination chemotherapy. Single agent chemo did not benefit. Effect similar irrespective of age, sex, stage or performance status. Non-responders 25%; partial response 50%; complete pathological response 25%. Similar findings in Canadian study 2004.

Adjuvant chemotherapy
Administration of systemic chemotherapy to a group of patients after definitive treatment with the intention of reducing the likelihood of relapse and death
Few quality randomised trials, all containing small numbers, with confusing methodology and analysis
Best evidence from ABC group, comprising 6 trials (all cystectomy) of 498 patients.
  - 9% improvement in OS (59% vs. 50%)
  - 12% improvement in DFS (62% vs. 50%)
However difficult to draw definitive conclusions given quality of assessed data

Down-staging chemotherapy
Administration of systemic chemotherapy to a group of patients with inoperable disease with the intention of facilitating a cure with subsequent definitive treatment
Few studies as most patients ineligible
MSKCC reported results of post-chemotherapy surgery in 80 patients after MVAC (Herr 2001).
  - Best outcome in patients with regional mets or T4 disease and with complete responses to chemotherapy
  - 40% with complete radiological remission had residual disease at cystectomy; 20% with radiological evidence were T0
  - 29% alive at 5 years
Management of metastatic bladder cancer

Local radiotherapy
Indications
- Haematuria: 21 Gy in 3 fractions (alternatively 30-35 Gy in 10 fractions)
- Hypofractionation a/w increased gut morbidity but equally effective (Duchesne 2000)
- Can be used in patients with extravesical pelvic mets

Bone mets

Systemic chemotherapy
Overall response rate with complete remissions in 40-70%
Median overall survival 12-14 months
- Visceral mets: 15% patients
- Lymph nodes only: 30% patients

15-20% patients experience long-term survival with chemotherapy alone

Poor prognostic factors
- Poor performance status (Karnovsky <80%)
- Visceral metastases (lung, liver, bone)

Chemotherapy regimes:
- MVAC (methotrexate, vincristine, adriamycin, cisplatin) more effective than single agent cisplatin but higher toxicity (Loehrer 1992)
- High dose MVAC (aka accelerated MVAC) administered with GM-CSF a/w improved response rates, lower toxicity and improved survival vs. ordinary MVAC but more expensive (14 months vs. 8 months)
- GemCis a/w similar survival rates cf. MVAC but with improved side-effect profile (neutropenia, neutropenic sepsis, alopecia and mucositis) and lower toxic death rate (1% vs. 3%) (Von der Maase 2000) One cycle of GemCis given over a period of 15 days, repeated every 28 days for maximum of 6 cycles. One cycle of MVAC given over 22 days, repeated every 28 days for a maximum of six cycles – effectively a maximum of 6 months therapy. Can still give palliative GemCis if already had 3 cycles of neoadjuvant GemCis

New regimes
- Cisplatin, gemcitabine and taxol a/w overall response rate of 77.6% and a complete response rate of 27.6% in a small number of patients with previously untreated disease (Bellmunt, Guillem et al. 2000) Currently being trialed vs. GemCis by EORTC.
- Carboplatin can be given for patients with GFR < 60 ml/min
- Oxaliplatin not renally excreted and better efficacy than carboplatin
- Erlotinib (Lamm trial) and sunitinib (Succint) awaited

MVAC failures
- Gemcitabine and paclitaxel a/w median survival rates of 14.4 months in MVAC failures (Sternberg 2001)
Follow-up after treatment with curative intent

Rationale
Early detection of local recurrence and distant metastasis may guide potential salvage therapy, including salvage cystectomy, urethrectomy, nephroureterectomy and chemotherapy
Efficacy and cost-effectiveness of follow-up regimens not well characterised

EAU recommendations
After Cystectomy
• Physical examination to exclude surgical complications
• Serum creatinine and blood gas analysis to assess kidney function
• Urine analysis
• Sonography of the kidney, liver and retroperitoneum
• Chest-X-ray
In case of unremarkable findings regular follow-up in intervals of 4 months are indicated. In case of pN+ additional regular CT scans and bone scintigraphy are necessary. PTis patients need regular assessment of the upper urinary tract. Barbotage cytology is recommended for the remaining urethra.

After Radiotherapy
• Physical examination to exclude surgical complications
• Serum creatinine and blood gas analysis to assess kidney function
• Urine analysis
• Sonography of the kidney, liver and retroperitoneum
• CT scan of the pelvis
• Cystoscopy and urine cytology
• Chest-X-ray
The main interest during follow-up remains the bladder, because of the high local failure rate.

TJW follow-up regimen

Histology/post-op follow-up at 6 weeks
6 monthly follow-up with bloods, CXR, USS liver/kidneys
Flexible urethroscopy/pouchoscopy yearly
CT chest/abdo/pelvis yearly for 3 years
Check vitamin B12 levels at 3 years onwards
Bloods/CXR/USS years 4 and 5
Discharge at 5 years if well and no hydronephrosis/urethral recurrence
Appendix

Haematuria
Macroscopic haematuria  visible presence of blood in urine
Microscopic haematuria  3 or more rbcs per high power field in the urinary sediment of 2 of 3 properly collected specimens*

* upper limit of normal in volunteers $6 \times 10^5$ rbc over 12 hours – approximately 2 rbcs per high power field. Therefore a value of 3 indicates > 2 sd above norm. Prevalence of asymptomatic haematuria ranges from 0.3-30% dependent on population screened and method of detection

Haematuria Clinic
BAUS haematuria guidelines
Visible haematuria vs. non-visible haematuria
Non-visible haematuria classified symptomatic or asymptomatic
Dipstick haematuria = micro haematuria
Trace = negative; 1+ = positive
Haemolysis = non-haemolysed
Significant haematuria:
- Single episode visible haematuria
- Single episode symptomatic non-visible haematuria (UTI, menstruation, heavy exercise excluded)
- Persistent asymptomatic non-visible haematuria (2 of 3 dips positive)

All patients over 40 have primary urological assessment
Patients 40 yr or less with hypertension (>= 140/90), raised albumin/creatinine ratio (>=30) or eGFR < 60 ml/min refer for primary nephrology assessment

Imaging modalities
Controversial
Universally accepted that USS, KUB and flexible cystoscopy have a role in primary detection
A number of studies have shown that if IVU is omitted UT tumours would be missed

Khadra 2000 (Freeman hospital, Newcastle, n=1930) 2/1930 patients had UTUC; 1 had visible haematuria, one had non-visible haematuria, both were smokers.
Edwards 2006 (n = 4020). Largest study to date. 3/13 UT TCC and none of 60 RCC missed. Of the 3/4020 patients with UTUC not diagnosed on USS, no comment was made about their smoking status or NVH vs. VH presentation. No cytology [4.8% malignancies in patients with micro haematuria (1% RCC, 0.1% UT TCC, and 3.7% TCC), and 18.9% in those with gross haematuria (2% RCC, 0.5% UT TCC, 16.4% TCC).
Others have shown that, provided cytology is normal, and there is no loin pain or hydroureter, IVU may be safely omitted, thereby avoiding up to 2.5% contrast reactions (Datta 2002; n=1000).

Other issue is whether cytology should form part of initial assessment, both for upper and lower tract TCC; one study has shown that of 69/106 (out of 35,000 screened) patients with cytology +ve/cystoscopy –ve patients had CIS on biopsy (Farrow 1977). However very old study. Recent evidence has shown that cytology may safely be omitted from haematuria assessment without compromising cancer detection rate.

Bladder cancer screening

Remember Wilson and Junger criteria (10)

- Important health problem
- Natural history should be understood
- Recognisable latent or early phase
- There needs to be a suitable test to examine for the disease
- Screening test must be acceptable to the population
- Treatment must be acceptable
- Agreed policy on whom to treat as patients
- Facilities for diagnosis and treatment available
- Screening must be repeated according to natural history
- Cost should be economically balanced

Most importantly, screening needs to change the natural history of the disease i.e reducing morbidity or mortality. Randomisation crucial to avoid selection bias, lead-time bias, and to examine the effect of detection of indolent cancers etc.

To date no prospective randomized controlled trial of screening for bladder cancer

2 very similar studies in Wisconsin (Messing 1992;1995) and Leeds (Britton 1989; 1992) performed on unselected middle-aged males using repeated reagent-strip testing (10-14 tests)

- Overall 20% had dipstick haematuria at least once
- Of those undergoing urological evaluation 6-8% had urothelial tumours (1.2% of patients overall)
- Messing data compared screened group with local cancer registry. Similar proportions of high-grade and low-grade disease in each group, but much higher incidence of muscle-invasion in non-screened group, which translated into reduced mortality in screened group on long-term follow-up

Above results have not been repeated

Cost effectiveness depends upon prevalence of asymptomatic haematuria in screened population (itself dependent on type of testing), the incidence of urothelial disease in screen-positive cases, and cost of investigation vs. cost of ‘delayed diagnosis’. Minimal data on this.
**BCG Toxicity**

*Bacillus Calmette-Guerin* - live attenuated strain of mycobacterium

Contact binding of BCG to epithelium (? via fibronectin) stimulates tumour cell internalisation. Cells release IL-12 and stimulate TH1 cell immunological response.

Treatment of choice for high-grade disease

Reduces recurrence and progression

Contraindicated in immunosuppressed/ immunocompromised

Side effects due to BCG common and often poorly tolerated. In SWOG study of maintenance vs. induction only (Lamm 2000) less than 50% completed 3 cycles (12 months), 25% had grade 3 toxicity, and only 16% (1 in 6) completed three years.

Side effects (Including Lamm 1992 n=2602 - largest study to date 50mg BCG)

- Irritative bladder symptoms & dysuria: 95%
- Haematuria: 30%
- Fever > 39 C: 3%
- Granulomatous prostatitis: 1% (20% silent)
- Sepsis: <1%
- Hepatitis: <1%
- Pneumonitis: <1%
- Allergic reaction: <1%
- Ureteral obstruction: <1%
- Contracted bladder: <1%
- Death (usually sepsis/MOF): 1 in 12,500

**Irritative bladder symptoms** and haematuria usually occur at 3 weeks. Often accompanied by flu-like symptoms, fever less than 38.5, lasting less than 48 hours. Treatment symptomatic with analgesia, paracetamol and anticholinergics. No requirement for cessation of BCG

**Allergic side effects** (conjunctivitis/arthralgia) typically 5 weeks. Treated with antihistamines. No requirement for cessation of BCG unless symptoms persist for more than 7 days. Then treat as for BCG infection

**Epididymitis** and symptomatic granulomatous prostatitis: Treat with INH and RFP for 3 months with or without fluoroquinolones

**BCG sepsis** most feared complication. Arises secondary to BCG absorption particularly in presence of UTI or traumatic catheterisation. A/w fever >= 39, rigor, mental confusion and hypotension. May progress to DIC and MOF. Responsible for most deaths in literature. Cultures typically negative, and may be related to delayed hypersensitivity reaction.

**Mx**

- Isoniazid: 300mg od
- Rifampicin: 600mg od
Ethambutol 1200 mg od  
Prednisolone 40 mg od  
Supportive therapy

NB. *M Bovis* insensitive to pyrazinamide

**Pneumonitis** may occur alone or with hepatitis. Presents with low grade fever, SOB and malaise. Admit for bloods, CXR, and Rx with resuscitation, INH and RFP for six months. Severe cases also get ethambutol and steroids. NB. CXR may show only fine reticular pattern despite severe CT appearance. Aetiology unclear. ZN staining, culture and PCR occasionally implicate actual infection, but often no organisms are found, suggesting a type IV hypersensitivity reaction.

![Image of chest X-ray and CT scan]

**Mechanisms to reduce BCG toxicity**

One-third dose (27mg) compared to standard dose (81mg) in large randomized trial (n=500) by Spanish Oncology Group (CUETO; Martinez-Pineiro 2002). No difference in recurrence or progression rates, with reduced overall toxicity in low dose group. However incidence of severe toxicity similar and recurrence rate of multifocal tumours lower in normal BCG dose group.

NB. No difference in strains of BCG in terms of efficacy or toxicity

**Mitomycin C**

Cross-linking cytotoxic agent, originally isolated from *streptomycyes lavendulae*. Inhibits DNA synthesis (G1) via cell-cycle dependent and independent means. High molecular weight ~330 kD

- Good evidence that single instillation post-TUR reduces recurrence (see below)
- Average reduction in recurrence with 6-weekly instillations ~15% vs. TUR alone
- No evidence that MMC alters progression
- Side effects include chemical cystitis (40%), decreased bladder capacity, palmar desquamation, and skin rashes.
Doxirubicin
Anthracycline antibiotic. Binds DNA, inhibits topoisomerase II, and retards protein synthesis
13-17% reduction in recurrence with six instillations vs. TUR alone
No effect on progression
Chemical cystitis predominant side effect
Epirubicin-related molecule with similar characteristics. In addition to reducing recurrence in high risk disease, also proven to reduce recurrence ~ 50% as a single post-TUR instillation (see below).

Thiotepa
Triethylenthiophosphoramide
Originally reported to be efficacious in the 1960s
Meta-analyses show ~16% reduction in recurrence rates cf. TUR alone
Lower molecular weight cf. other cytotoxics. Up to one third of drug absorbed through urothelium.
Leucopenia and thrombocytopenia (myelosuppression) problematic with multiple doses

Valrubcin
Semi-synthetic analogue of doxorubicin
21% complete response in patients with BCG refractory carcinoma-in-situ
Currently undergoing trials in cystectomy-unfit patients in US

Interferon
Endogenous glycoprotein with anti-tumour actions (anti-tumorigenesis, cytokine release, and activated T/B cells)
Interferon alpha 2b used for intravesical therapy
Optimum dose unknown. Given at 50-100 million units per instillation
Decreased recurrence rates in high risk superficial disease but << BCG
BCG-IF combination therapy reportedly superior than BCG alone but small, phase I study. (Bercovich 1995)

Keyhole Limpet Haemocyanin
Non-specific immuno-stimulant derived from KL mollusc
First reported to be efficacious in bladder cancer in 1974
Small studies report superior reduction in recurrence rate cf. mitomicin.
Poor efficacy cf. BCG but much less toxic.
Provokes mild fever
May retain role as an immuno-modulator