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 of 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

Painless haematuria	Very common 85% of patients (however in patients with a cystoscopically detectable lesion, haematuria is almost always found if enough specimens are taken)
Irritative LUTS	Occasional almost never occur without haematuria
Flank pain	Uncommon
Lower limb oedema	Uncommon
Pelvic mass	Uncommon
Weight loss	Rare
Bone pain	rare
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

<u>Transitional cell carcinoma</u>
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 2: WHO grading in 1973 and in 2004 (7,8)

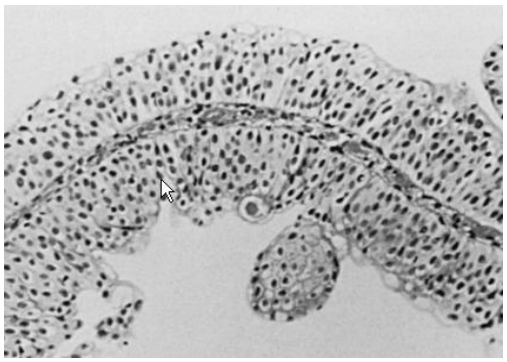
1973 WHO grading	
Urothelial papilloma	
Grade 1:	well differentiated
Grade 2:	moderately differentiated
Grade 3:	poorly differentiated
2004 WHO grading	
Urothelial papilloma	
Papillary urothelial neoplasm of low malignant potential (PUNLMP)	
Low-grade papillary urothelial carcinoma	
High-grade papillary urothelial carcinoma	

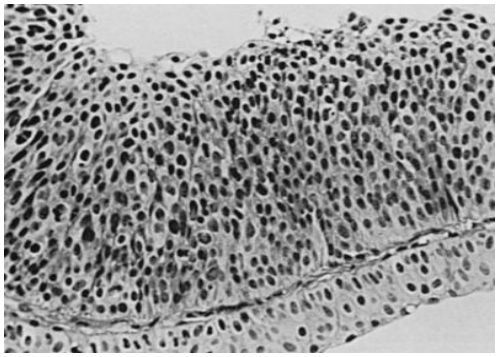
Papilloma — papillary lesion with a fine fibrovascular core covered by normal bladder mucosa. Normal layers and no cytological abnormalities. Extremely rare. If solitary and no co-existent TCC can be considered benign.

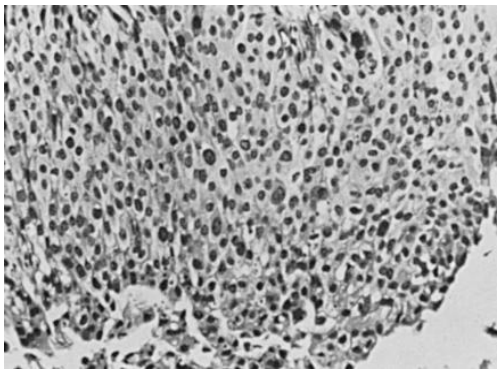
PUNLMP — Old grade 1
thin fibrovascular stalk with a thickened urothelium containing more than seven cell layers
slight anaplasia and pleomorphism with rare mitotic figures.
often recur, and recurrences may be of higher histologic grade and stage

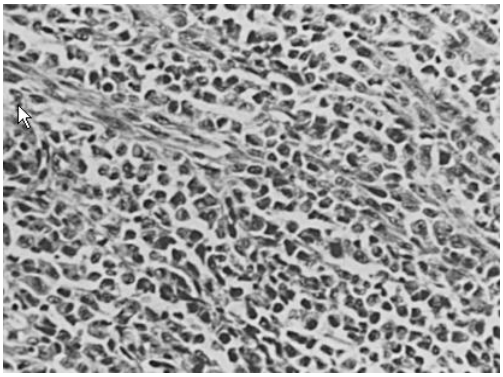
LGPUC — Old grade 2
Wider fibrovascular core, greater disturbance of the base-to-surface cellular maturation, and a loss of cell polarity. The nuclear-cytoplasmic ratio is higher, with more nuclear pleomorphism and prominent nucleoli. Mitotic figures are more frequent. May be difficult to differentiate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


Papilloma


PUNLMP


LGPUC


HGPUC

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)
- p 21
  - 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

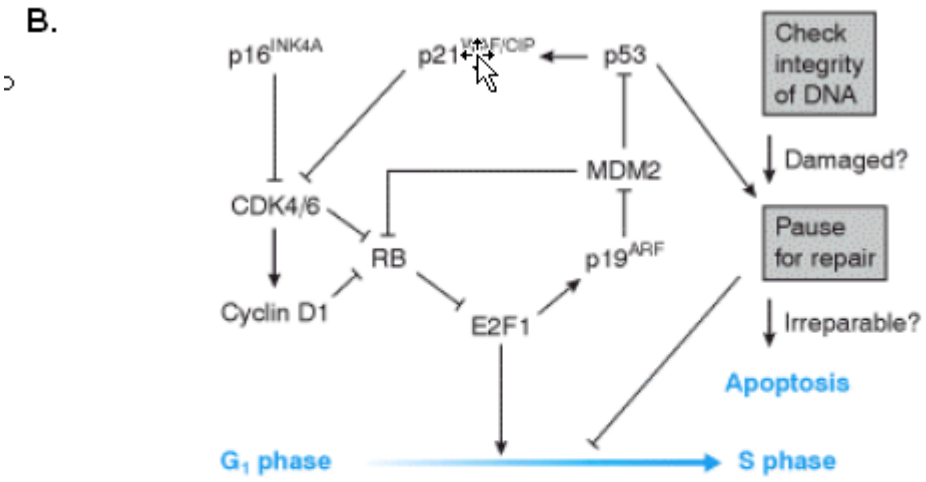


Fig. 1.2 Regulation of cell-cycle G1/S checkpoint
A. Schematic representation of the eukaryotic cell cycle. During G1, cells increase in size, produce RNA and synthesise proteins in readiness for DNA synthesis. The G1/S checkpoint represents an important regulatory mechanism ensuring defective cells 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 $p21^{WAF/CIP}$ 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)

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

T - Primary tumour		
TX	Primary tumour cannot be assessed	
T0	No evidence of primary tumour	
Ta	Non-invasive papillary carcinoma	
Tis	Carcinoma in situ: 'flat tumour'	
T1	Tumour invades subepithelial connective tissue	
T2	Tumour invades muscle	
T2a	Tumour invades superficial muscle (inner half)	
T2b	Tumour invades deep muscle (outer half)	
T3	Tumour invades perivesical tissue:	
T3a	Microscopically	
T3b	Macroscopically (extravesical mass)	
T4	Tumour invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall	
T4a	Tumour invades prostate, uterus or vagina	
T4b	Tumour invades pelvic wall or abdominal wall	
N - Lymph nodes		
NX	Regional lymph nodes cannot be assessed	
N0	No regional lymph node metastasis	
N1	Mestatasis in a single lymph node 2 cm or less in greatest dimension	
N2	Metastasis in a single lymph node more than 2 cm but not more than 5 cm in greatest dimension, or multiple lymph nodes, none more than 5 cm in greatest dimension	
N3	Metastasis in a lymph node more than 5 cm in greatest dimension	
M - Distant metastasis		
MX	Distant metastasis cannot be assessed	
M0	No distant metastasis	
M1	Distant metastasis	

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 metastatses
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 @ 3 yrs

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 1 – Weighting used to calculate recurrence and progression scores

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

Table 2 – Probability of recurrence and progression according to total score*

Recurrence score	Probability of recurrence at 1 yr (95% CI)	Probability of recurrence at 5 yr (95% CI)	Recurrence risk group
0	15% (10–19%)	31% (24–37%)	Low risk
1–4	24% (21–26%)	46% (42–49%)	Intermediate risk
5–9	38% (35–41%)	62% (58–65%)	
10–17	61% (55–67%)	78% (73–84%)	High risk
Progression score	**Probability of progression at 1 yr (95% CI)**	**Probability of progression at 5 yr (95% CI)**	**Progression risk group**
0	0.2% (0–0.7%)	0.8% (0–1.7%)	Low risk
2–6	1% (0.4–1.6%)	6% (5–8%)	Intermediate risk
7–13	5% (4–7%)	17% (14–20%)	High risk
14–23	17% (10–24%)	45% (35–55%)	High risk

CI = confidence interval.

* An electronic calculator for recurrence and progression scores is available at http://www.eortc.be/tools/bladdercalculator/.

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

Dipstick haematuria	Sensitivity	40 – 92%
	Specificity	51 – 96%
	False negatives arise as haematuria intermittent in 25%	
Cytology	Sensitivity	28 – 76% (esp. poor in low-grade)
	At best, still misses ~20% high grade lesions	
	Specificity	81-100%
Cystoscopy	Reference standard for studies of markers	
	Surprisingly high false negative rates reported (10-40%)	
	Specificity fairly low ~ 40%	

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 (Konety 2006)

Table 1
Sensitivity and specificity of urine based bladder markers

Bladder cancer marker [references]	Mean sensitivity (range)	Mean specificity (range)
Cytology [7,9,10,13,7,30–46]	48.00% (28%–76.47%)	95.72% (81%–100%)
NMP22 [9,10,20,24,26,28,30,32,40–55]	67.49% (31%–91.7%)	74.38% (5.1%–94.3%)
BTA stat [6,8,30,33,36,49,56–63]	68.71% (52.8%–89%)	73.67% (54%–93%)
BTA TRAK [5,25,33,49,59,64–66]	61.96% (17%–77.5%)	73.59% (50.5%–95%)
Telomerase [4,6,9,13,67–71]	72.4% (46%–92%)	87.15% (69%–99%)
Hyaluronic acid and hyaluronidase [62,72,73]	94% (91%–100%)	80.93% (70%–88.8%)
Flow cytometry and Quanticyt™ assay [28,30,35,37,74]	58.08% (45%–72%)	80.62% (70.6%–93%)
Fluorescence in situ hybridization [6,37,75]	77% (73%–81%)	98% (96%–100%)
ImmunoCyt™ [39,75–77]	58.2% (38.5%–86.1%)	78.77% (73%–83.9%)
Cytokeratin 20 [38,78–82]	82.83% (71%–94.4%)	73.37% (36%–96.7%)
Cytokeratins 8 and 18 (UBC) [33,51–53,83]	60.7% (48.7%–70%)	83.82% (72%–95%)
Lewis X antibody [34,61]	87.1% (79.8%–94.4%)	61.65% (36.9%–86.4%)
Hemoglobin dipstick [4–7]	71.2% (47%–92.6%)	67.27% (51%–84%)
CYFRA 21-1 [51,84]	74.15% (69%–79.3%)	91.3% (88.6%–94%)
Survivin [85]	64%	93%

Screening:

No single test considered effective for screening for bladder cancer

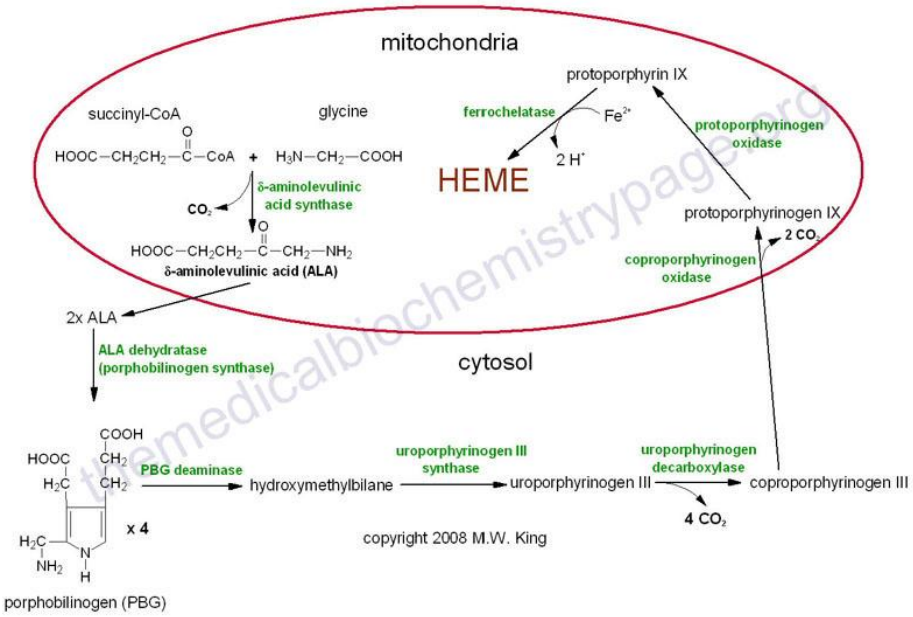
Repetitive haematuria testing has been shown in non-randomised setting to be associated with improved survival cf. observational non-screened group.(Messing 1992; Britton 1989 (Leeds, UK)). A number of markers have high sensitivities (hyaluronidase/hyaluronic acid, BLCA4, microsatellite repeats, telomerase) 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.

<u>Photodynamic diagnosis</u>



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

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 3 – PDD using 5-ALA versus conventional WLC: long-term follow-up

Author	No. of patients available for efficacy analysis	Recurrence-free survival rate, %		Median follow-up, mo	
		PDD	WLC	PDD	WLC
Daniltchenko [39]	102	41	25	42	39
Denzinger [37]	191	71	45	86	83

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

   - Studies utilising MMC appear to show no difference in recurrence rates
4. Cost effective

<u>Problems</u>

- 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

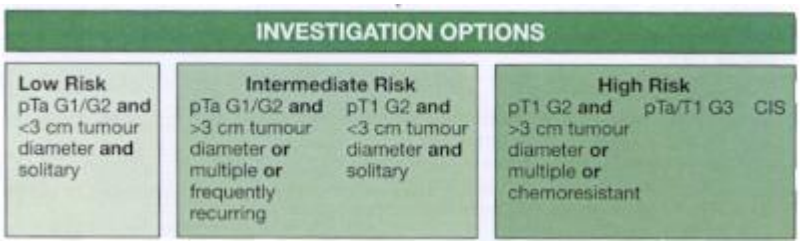
Ta, T1G1, T1G2	5-8% progression
T1G3	50% progression

<u>Risk Stratification</u> (slightly different for EAU, AUA and NCCN and BAUS Oncology)

	Definitions		
	Low risk	Intermediate risk	High risk
EAU [1]	G1-2Ta Low risk of tumour recurrence and progression (EORTC recurrence score = 0; progression score = 0)	Multifocal G2Ta, G1T1, solitary G2T1 Intermediate or high risk of recurrence and intermediate risk of progression (EORTC recurrence scores ranging from 1–9; progression scores ranging from 1–6)	Multifocal G2T1, G3Ta-T1, CIS High risk of progression (EORTC progression scores ranging from 7–23)
FICBT [9–11]	Low-grade Ta	Low-grade Ta with high risk factors for recurrence or recurrent low-grade Ta tumours	High-grade Ta, all T1, CIS
NCCN [3]	G1-2Ta	G3Ta, solitary G1-2T1	Multifocal T1, G3T1 (CIS listed separately)
AUA [4,5]	Small volume, low-grade Ta	Multifocal and/or large volume low-grade Ta High risk of recurrence, low risk of progression	High-grade Ta, all T1, CIS

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	
	At 1 yr	At 5 yrs	At 1 yr	At 5 yrs
Solitary pTa G1	15%	31%	0.2%	0.8%
Solitary pTa G2	24%	46%	0.2%	0.8%
Multifocal pTa G1	24%	46%	1%	6%
Multifocal pTa G2	24%	46%	1%	6%
Solitary pTa G3	24%	46%	1%	6%
Solitary pT1 G2	24%	46%	1%	6%
Multifocal pTa G3	38%	62%	5%	17%
Multifocal pT1 G2	38%	62%	5%	17%
pT1 G3 no CIS	24%	46%	5%	17%
pT1 G3 with CIS	24%	46%	17%	45%
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

<u>BCG failure</u>

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 Peristence 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 acheiving 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)

Peristence of high-risk disease at 6 months should be considered for radical cystectomy (radical radiotherapy no place in management of high-risk superficial

disease)
Options for unfit patients:

(i) <u>BCG and interferon</u>

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) <u>Sequential electromotive BCG/MMC</u>

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.

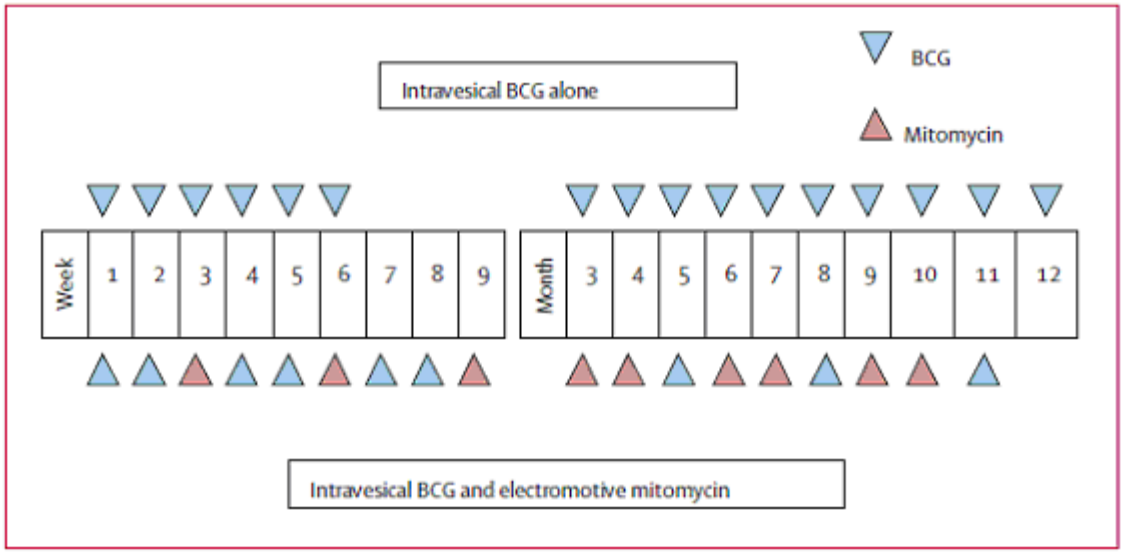


Figure 1: **Dose schedules**

(iii) <u>Thermotherapy</u>

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 cystocopies 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/ 3month 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/m^2 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)

<u>Selective bladder preservation</u>
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).

Series	Stages	N	Overall survival	
Cystectomy			5yr	10yr
USC (Stein et al 2001)	P2-P4a	633	48	32
MSKCC (Dalbagni et al 2001)	P2-P4a	181	36	27
Selective bladder preservation				
Erlangen (Rodel et al 2002)	cT2-4	326	45	29
MGH (Shipley et al 2001)	cT2-4a	190	54	36

<u>Radical cystectomy</u>

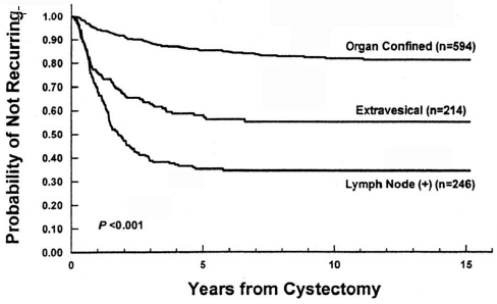
Indications: T2-T4a, N0-Nx, M0
High-risk superficial bladder cancer

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)

Stage T0 80% 10 YS (Johns Hopkins)
Stage T2 70% 5YS
Stage T3 35% 5YS
Stage T4 25% 5YS

* 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-naiive 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)

G3pT1	5-10%
pT2	10-30%
pT3	30-65%

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

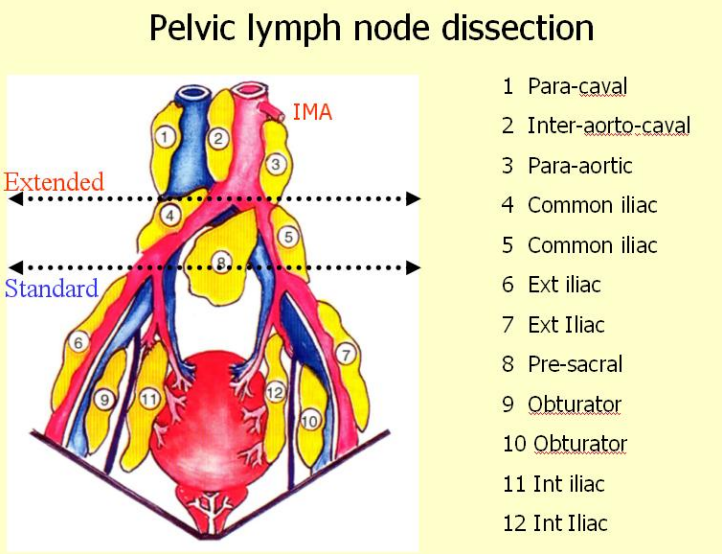
Limited LND	obturator packet only
Standard	below common iliac bifurcation
Extended	2cm above aortic bifurcation to origin of IMA

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 4. *Log rank analysis indicating cancer specific survival of patients who were followed a minimum of 2 years according to stage at diagnosis and number of lymph nodes*

	Stage			
	In Situ/I	II	III	IV
No. lymph nodes (%):				
0	68.6	60.2	42.7	32.6
1–3	85.7	70.6	42.9	29.6
4–6	100	88.2	60.5	35
7–9	100	68.2	46.2	46.2
10–14	100	82.6	81.5	49
15–19	90	75	64.7	39
20 or Greater	100	72.7	60	41.7
No. pts.	138	210	243	395
p Value	0.0147	0.0898	0.0237	0.0046

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-Latief 2004

<u>Role of urethrectomy in males</u>

Overall risk of urethral recurrence 8.1% (Stenzl 2002 – metaanalysis 3165 pts)
Median time to urethral recurrence 2 years
Historically, multifocallty, 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 fozen 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

<u>Role of urethrectomy in females</u>
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

<u>Prostate-sparing cystectomy</u>
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)

Continence rates drop sharply in all patients over 70 yrs

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.

Type	Reservoir	Conduit	Sphincter
Ilial conduit	-	ileum	-
Mainz ureterosigmoidostomy	sigmoid	-	Anal
Indiana continent pouch	caecum		iliocaecal valve
Ileal neobladder	ileum	urethra	ext. urinary

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 21Gy 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 x 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 hydronephrosis, 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 assesment without compromising cancer detection rate.

<u>Bladder cancer screening</u>

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 analgaesia, paracetomol 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

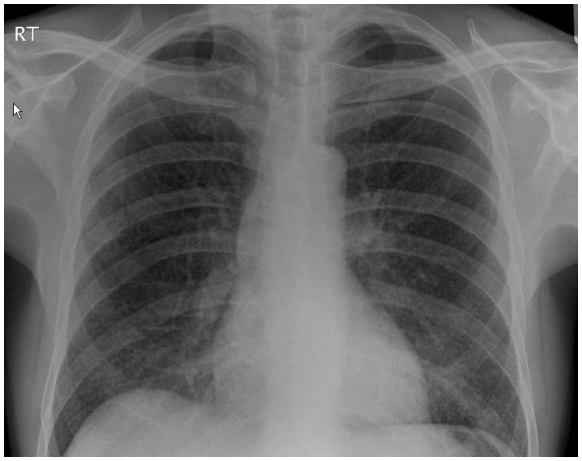
BCG sepsis most feared complication. Arises secondary to BCG absorption particularly in presence of UTI or traumatic catheterisation. A/w fever >= 39, rigor, mental confusion and hypotension. May progress to DIC and MOF. Responsible for most deaths in literature. Cultures typically negative, and may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

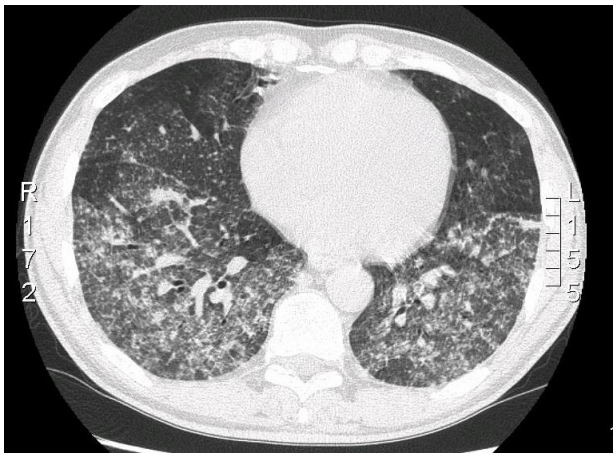
Mx	Isoniazid	300mg od
	Rifampicin	600mg od

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.





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 *stremtomyces 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
Triethylenethiophosphoramide
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

Valrubicin
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