Bladder Cancer

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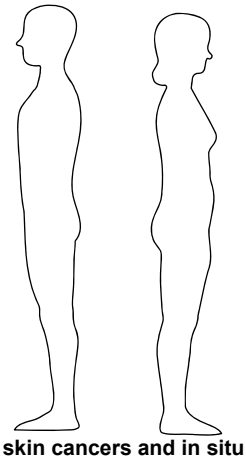
Objectives

- **Bladder Cancer**
  - **Epidemiology**
  - **Pathology**
  - **Risk factors**
  - **Presentation and clinical findings**
  - **Staging**
  - **Natural history**

2012 Estimated New Cancer Cases*

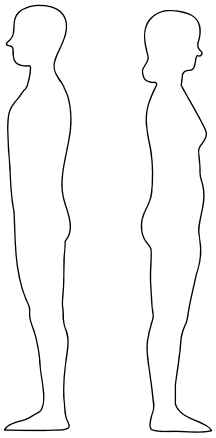
Men 848,170	Women 790,740
Prostate	Breast
Lung & bronchus	Lung & bronchus
Colon & rectum	Colon & rectum
Urinary bladder	Uterine corpus
Melanoma of the skin	Thyroid
Kidney & renal pelvis	Melanoma of the skin
Non-Hodgkin lymphoma	Non-Hodgkin lymphoma
Oral cavity & pharynx	Kidney and renal pelvis
Leukemia	Ovary
Pancreas	Pancreas
All Other Sites	All Other Sites



*Excludes basal and squamous cell skin cancers and in situ carcinomas except urinary bladder.
Source: American Cancer Society, 2012

2012 Estimated Cancer Deaths

Men 301,820	Women 275,370
Lung & bronchus	Lung & bronchus
Prostate	Breast
Colon & rectum	Colon & rectum
Pancreas	Pancreas
Liver & intrahepatic bile duct	Ovary
Leukemia	Leukemia
Esophagus	Non-Hodgkin lymphoma
Urinary bladder	Uterine corpus
Non-Hodgkin Lymphoma	Liver & intrahepatic bile ducts
Kidney & Renal Pelvis	Brain & other nervous system
All other sites	All other sites



Source: American Cancer Society, 2012

Epidemiology

- **Bladder cancer in the United States:**
  - **Estimated 73,510 new cases and 14,880 cancer related deaths in 2012**
  - **Whites > Blacks (2:1)**
  - **M>F (3-4:1)**
  - **A disease of the elderly (6^{th}-7^{th} decades)**
  - **Rising incidence (20% over the last 20-yr)**

Epidemiology

- **In U.S., the second most prevalent cancer in men≥60**
- **Bladder cancer has significant financial impact on healthcare**
  - **Requires intensive, life-long cystoscopic, radiologic, and cytologic surveillance**
  - **Most expensive malignancy in the U.S.***

*** Botteman MF, et al. *Pharmacoeconomics* 21:1315; 2003**

Bladder Cancer Pathology: Histologic Subtypes in the U.S.

- 90-95% Transitional Cell Carcinoma
- 3% Squamous Cell Carcinoma
- 2% Adenocarcinoma
- 1% Small Cell Carcinoma
- 1% Others

Risk Factors

- Gene abnormalities
- Chemical exposure
- Chronic irritation

Risk Factors

- Gene abnormalities
  - Proto-oncogenes: Ras
  - Tumor suppressor genes: p53, pRB, p16, p21, p27
  - Cell cycle regulatory proteins: cyclin D1
  - Tumor-specific growth factor pathways, angiogenesis and COX-2

Risk Factors

- Chemical exposure
  - Tobacco (rich in aromatic amines and acrolein)
  - Industrial contact to chemicals, plastics, coal, tar, asphalt, aromatic amines, aniline dyes, nitrites, and nitrates
  - Ifosfamide and Cyclophosphamide (long-term use)
  - Analgesic abuse, particularly phenacetin

Risk Factors

- Chronic irritation
  - Indwelling catheters, calculi (SCC)
  - Schistosoma haematobium (SCC, TCC)
  - Irradiation (SCC)

Signs and Symptoms

- Hematuria
  - Gross or microscopic
- Irritative symptoms
  - Frequency
  - Dysuria
  - Urgency
- Bladder outlet obstruction
- Ureteral colic

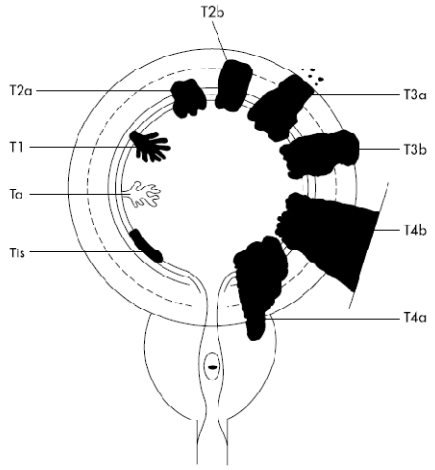
Physical Findings

- Palpable mass
- Bladder fixation to the pelvic wall
- Prostate induration
- Related to metastatic disease

Diagnostic Testing

- Urine Cytology (Sensitivity 67%, specificity 96%)
- Cystoscopy
  - Transuretheral resection of bladder tumor (TURBT)
  - Ureteroscopy
  - Retrograde pylography
- Radiographic Imaging (CT, MRI, IVP)
- Bone Scan (if elevated Alk Phos or bone pain)

TNM Staging of Bladder Cancer



Colquhoun AJ, et al.
Postgrad Med J. 2002

TNM Staging, cont.

- Nodal disease
  - N1 Single regional LN mets in the true pelvis (hypogastric, obturator, external iliac, or presacral LN)
  - N2 Multiple regional LN mets in the true pelvis
  - N3 LN metastasis to the common iliac LNs
- Metastatic disease
  - M0 no distant mets
  - M1 distant mets

American Joint Committee on Cancer (AJCC); 7th ed., 2010

TNM Staging, cont.

- 0 Ta, Tis
- I T1 only
- II T2a, T2b
- III T3a, T3b (perivesical tumor)
  T4a (prostate, uterus or vagina)
- IV T4b (pelvic or abdominal wall)
  Any N or M

Stages at Presentation

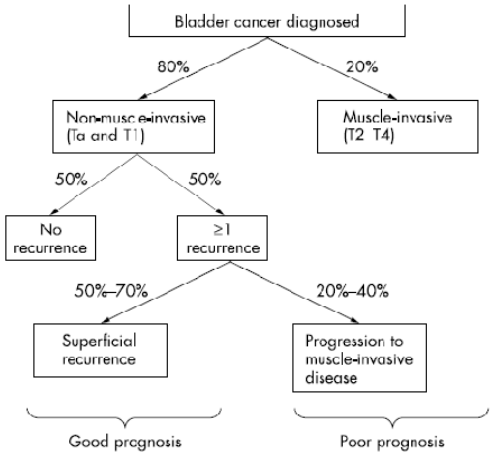
- 75% Superficial cancer
- 20% Muscle-invasive cancer
- 5% Metastatic disease

Bladder Cancer Stage: Prognosis

Location	Stage	T - N - M			Survival (5 yrs)
Superficial	0a 0is	Ta Tis	N0	M0	> 80 %
Lamina	I	T1	N0	M0	60-80 %
Early Muscle	II	T2a	N0	M0	30-50 %
Deep Muscle	II	T2b	N0	M0	20-40 %
Perivesical Fat	III	T3	N0	M0	15-25 %
Lymph Nodes	IV	Any T	N1-3	M0	5-20 %
Metastatic	IV	Any T	Any N	M1	< 2 %

AJCC Cancer Staging, 1998

Natural History of Bladder Cancer



Colquhoun AJ, et al.
Postgrad Med J. 2002

Superficial Bladder Cancer

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Objectives

- **Superficial Bladder Cancer**
  - **Surgical management**
  - **Prevention of recurrence and progression**
    - **Intravesical chemotherapy**
    - **Intravesical immunotherapy**
  - **Surveillance: Follow-up and early detection of recurrence**

Bladder Cancer Staging Superficial Cancer

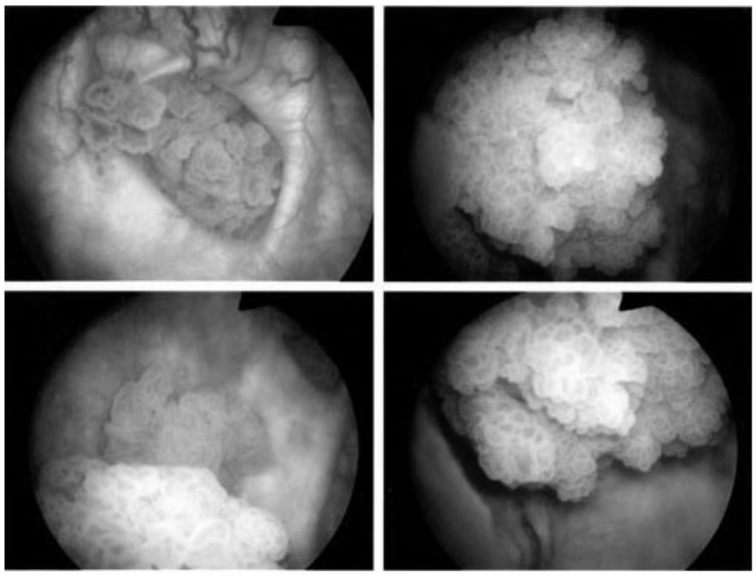
American Joint Committee on Cancer (AJCC)
TNM Staging System For Bladder Cancer

Primary Tumor (T)

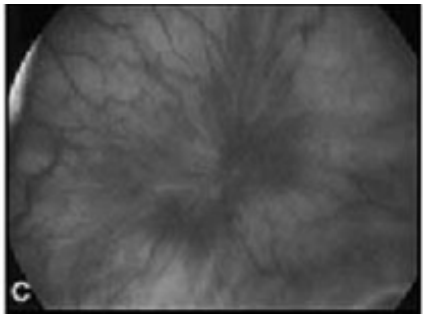
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Noninvasive papillary carcinoma
Tis	Carcinoma *in situ*: "flat tumor"
T1	Tumor invades subepithelial connective tissue
T2	Tumor invades muscle
T2a	Tumor invades superficial muscle (inner half)
T2b	Tumor invades deep muscle (outer half)
T3	Tumor invades perivesical tissue
T3a	Microscopically
T3b	Macroscopically (extravesical mass)
T4	Tumor invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall
T4a	Tumor invades prostate, uterus, vagina
T4b	Tumor invades pelvic wall, abdominal wall

AJCC Cancer Staging Manual 7th Edition

Papillary Bladder Tumors

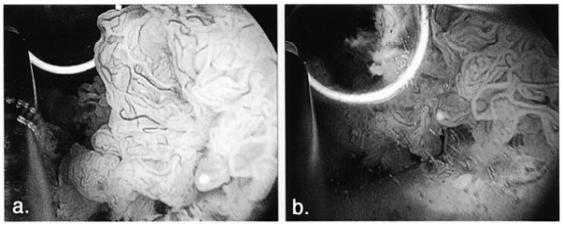


Flat Bladder Tumors (Carcinoma in situ (CIS))



- Most often is a flat red spot(s) in the bladder

Superficial Bladder Tumors Most Are Cured Endoscopically



- Transurethral resection (TUR) based on thermal energy
- May require more than one procedure for larger tumors

Cancer recurrence in the bladder
This is the real problem

% Recurrence
90
59
71
55
40
95
73
60
72
90
88
74

When the cancer comes back it may be worse
This is not as common but worsens prognosis

% Progression
4
18
2.4
3
7
39
16
10
25
52
39
30

European Organization for Research and Treatment of Cancer

Tables to Predict Bladder Cancer Recurrence and Progression

Predicting Recurrence and Progression in Individual Patients with Stage Ta T1 Bladder Cancer Using EORTC Risk Tables: A Combined Analysis of 2596 Patients from Seven EORTC Trials

Richard J. Sylvester [a,], Adrian P.M. van der Meijden [b], Willem Oosterlinck [c], J. Alfred Witjes [d], Christian Bouffioux [e], Louis Denis [f,1], Donald W.W. Newling [g,2], Karlheinz Kurth [h,3]*

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[g] Department of Urology, Free University Medical Center, Amsterdam, The Netherlands
[h] Department of Urology, Academic Medical Center, Amsterdam, The Netherlands

European Urology 49:466,2006

Recurrence and Progression Superficial Bladder Cancer

Factor	Recurrence	Progression
Number of tumors		
Single	0	0
2 to 7	3	3
≥8	6	3
Tumor size		
<3 cm	0	0
≥3 cm	3	3
Prior recurrence rate		
Primary	0	0
≤1 rec/yr	2	2
>1 rec/yr	4	2
T 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

European Urology 49:466,2006

Recurrence and Progression Superficial Bladder Cancer

	Probability of recurrence		Recurrence risk group
	at 1 yr % (95% CI)	at 5 yr % (95% CI)	
Recurrence score			
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)	Intermediate risk
10–17	61 (55–67)	78 (73–84)	High risk
	Probability of progression		Progression risk group
	at 1 yr % (95% CI)	at 5 yr % (95% CI)	
Progression score			
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.

European Urology 49:466,2006

FOCUS

- **Review of medical evidence on therapeutic opportunities to reduce tumor recurrence in superficial bladder cancer patients**

Therapeutic Opportunities Reducing Bladder Cancer Recurrence

- **Persistent/unrecognized tumor at the time of endoscopic resection of grossly visible tumors (residual cancer)**
- **Tumor implantation**
- ***Urothelial Field Change***

Residual Cancer After Endoscopic Resection

Variability in the Recurrence Rate at First Follow-up Cystoscopy after TUR in Stage Ta T1 Transitional Cell Carcinoma of the Bladder: A Combined Analysis of Seven EORTC Studies

Brausi, Maurizio; Collette, Laurence; Kurth, Karlheinz; van der Meijden, Adrian P.; Oosterlinck, Wm; Witjes, J.A.; Newling, Donald; Bouffioux, Christian; Sylvester, Richard J.

European Urology 41: 523 - 531, 2002

Promise of Improved Diagnostics

A New Generation of Optical Diagnostics for Bladder Cancer: Technology, Diagnostic Accuracy, and Future Applications

Evelyne C.C. Cauberg[a,], Daniël M. de Bruin[b], Dirk J. Faber[b], Ton G. van Leeuwen[b], Jean J.M.C.H. de la Rosette[a], Theo M. de Reijke[a]*

[a] *Department of Urology, Academic Medical Center Amsterdam, Amsterdam, The Netherlands*
[b] *Department of Biomedical Engineering and Physics, Academic Medical Center Amsterdam, Amsterdam, The Netherlands*

- **Photodynamic Diagnosis (PDD) – Fluorescence (ALA or HAL)**
- **Narrow-band Imaging (NBI)**
- **Optical Coherence Tomography (OCT)**

European Urology 56:287-297,2009

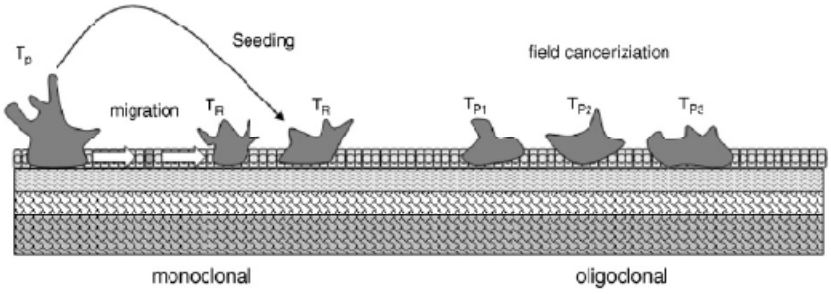
Improvements in Technology Lead to Better Outcomes

Repeat Endoscopic Resection Within 6 Weeks Reduces Tumor Recurrence

- **Many studies confirm for high grade tumors a repeat endoscopic resection of the area where the original tumor was removed often removes residual microscopic cancer and leads to better clinical outcomes**

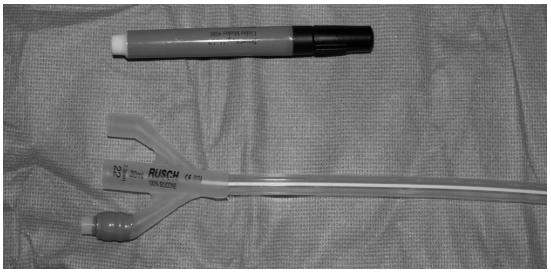
Tumor Implantation

Theories of Why Bladder Cancers Recur



Hoglund M, Seminars in Cancer Biology 17:225,2007

Single Dose Instillation of Chemotherapy After Surgery In The Bladder



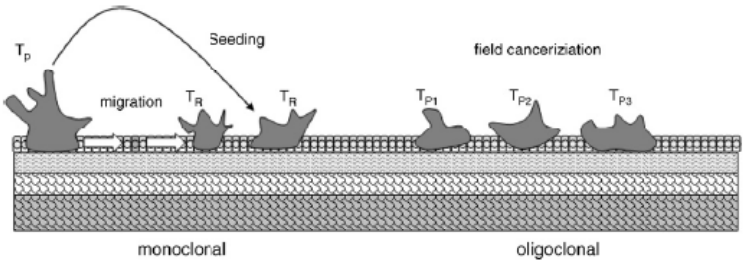
Single Dose Instillation of Chemotherapy In the Recovery Room After TUR

- Patients with a single tumor in the bladder reduced their risk of recurring from 47.1% to 35.8%
- Patients with more than one tumor in the bladder reduced their risk of recurring from 81.5% to 65.2%

Journal of Urology 171:2186–2190,2004

Urothelial Field Change

Field Defect – Slaughter's Concept of Field Cancerization



Hoglund M, Seminars in Cancer Biology 17:225,2007

Urothelial Field Change

- Rationale for the use of intravesical chemotherapy and immunotherapy
- Drugs administered in liquid form via a urethral catheter allowing direct instillation in to the bladder
- Drugs have a direct effect on the bladder epithelium (urothelium)

Reducing Risk of Recurrence Intravesical Chemotherapy Prophylaxis

Intravesical Chemotherapeutic Agents*

Thiotepa
Doxorubicin
Ethoglucid
Mitomycin C
Epirubicin
Valrubicin
Gemcitabine

***Wide range of doses and schedules – most common weekly for 6-8 weeks**

Reducing Risk of Recurrence Intravesical Immunotherapy Prophylaxis (BCG)

History of BCG Vaccine

- **BCG initially isolated by Calmette and Guerin (Pasteur Institute)**
- **Complete attenuation achieved through 231 sequential passages over 13 years (Mycobacterium bovis)**
- **Immunologists discovered the stimulatory effect of mycobacteria on the immune response to heterologous antigens (tumor cells)**
- **First tested in bladder cancer in the early 1980's**

New England Journal of Medicine 290:1413,1974

Bladder Cancer Recurrence Risk Adapted Groups To Determine What Drug Is Best

Low Risk

Intermediate Risk

High Risk

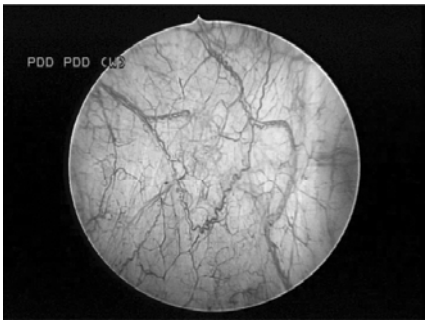
Maintenance Intravesical Therapy Reduces Cancer Recurrence

- **Some studies support periodically giving additional intravesical chemotherapy or BCG when the patient is tumor free for an extended period of time (1-3 years)**
- **As an example maintenance included 3 successive weekly intravesical instillations of BCG at 3,6,12,18,24,30 and 36 months (SWOG 8507)**

Bladder Cancer Follow-up
Detecting Recurrences

- **Office Cystoscopy**

Normal



Bladder Cancer Follow-up
Detecting Recurrences

- **Urinary Tumor Markers**
  - **Urine cytology**
  - **UroVysion FISH**
  - **NMP-22**
  - **BTA**

Summary of Typical Timeline of Management Superficial Bladder Cancer Patient

- Tumors removed by endoscopic resection in OR leading to cure
- One dose of intravesical chemotherapy given in the recovery room after surgery
- High probability of bladder cancer recurrence can be reduced by administering weekly intravesical chemotherapy or immunotherapy for a few weeks
- Maintenance intravesical therapy can further reduce the probability of cancer recurrence when the patient is tumor free

Muscle-Invasive and Advanced Bladder Cancer

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Objectives

- **Muscle-invasive and Advanced Bladder Cancer**
  - **Management of metastatic disease**
  - **Management of muscle-invasive disease**

Metastatic Disease

Introduction

- **Metastatic sites: regional and distant lymph nodes, lungs, bones, liver, brain, skin and elsewhere.**
- **Median survival with Best Supportive Care: 4-6 months**
- **Median survival with cisplatin-based combination chemotherapy: 12-14 months, 20% 3-yr survival**

Introduction

- **Many chemotherapy drugs have shown activity in bladder cancer, such as cisplatin, carboplatin, gemcitabine, methotrexate, vinblastine, doxorubicin, paclitaxel, docetaxel, ifosfamide, etc.**
- **TCC is a chemosensitive solid tumor**
  - **Phase II clinical trials: RR 70-80%**
  - **Phase III clinical trials: RR 50%**
- **Short duration of response: 4-6 mo**

Prognostic Factors & Survival Univariate and Multivariate Analysis (n=203) Bajorin, *JCO* 1999

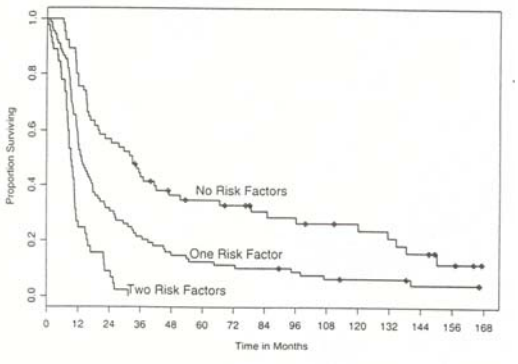
Prognostic Factors:

1) Visceral Metastases (bone, liver, lung)

2) Performance status (KPS) (<80%)

# of PF	MS (mo)	CR (%)
0	33	35
1	13.4	11
2	9.3	0

p = 0.0001



MSKCC data

Systemic Chemotherapy

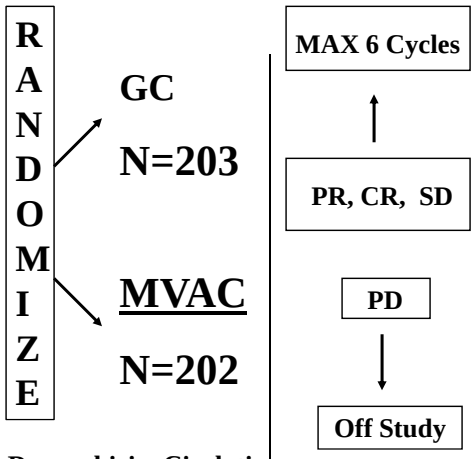
- **Till 2000, MVAC, the combination chemotherapy of methotrexate, vinblastine, doxorubicin, and cisplatin, was the standard of care for metastatic bladder cancer, based on phase II[(1)] and randomized phase III[(2, 3)] studies.**

(1) Sternberg C, et al. *J Urol* 1988
(2) Loehrer et al. *JCO* 10:1066, 1992
(3) Logothetis et al. *JCO* 8:1050, 1990

Advanced Bladder Cancer: Gemcitabine Plus Cisplatin vs. MVAC

Stratification

- Stage
- Visceral mets
- PS
- Prior radiotherapy
- Investigator site
- Disease measurability
- Alkaline Phosphatase



MVAC: **Methotrexate, Vinblastine, Doxorubicin, Cisplatin**

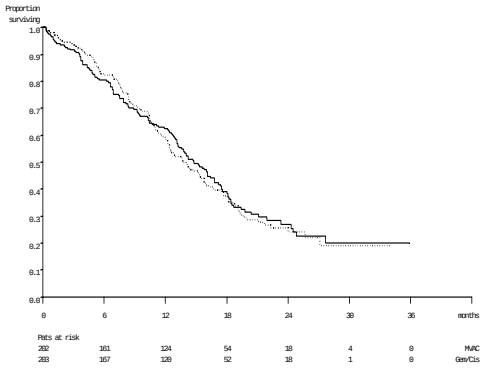
Von der Maase, JCO 2000

GC vs. MVAC
G3/4 Toxicities

	GC	MVAC
• Neutropenia (Grade 3/4)	71%	82%
Neutropenic sepsis	1%	12%
Febrile neutropenia	1.5%	13.4%
• Thrombocytopenia	57%	21%
• Mucositis	1%	22%
• Alopecia	11%	55%
• Nausea/vomiting	22%	21%
• Drug-toxicity death rate	1%	3%

GC vs. MVAC
Response and Survival

	GC (203)	MVAC (202)
• RR	49.4%	45.7%
– CR	12.2%	11.9%
– PR	37.2%	33.8%
• MS	13.8 (12.3-15.8)	14.8 (13.2-16.8)



Von der Maase, JCO 2000

Summary

- **Cisplatin-based combination chemotherapy improves survival for patients with advanced bladder cancer.**
- **First-line treatment**
  - **Good PS, adequate GFR: Cisplatin-based**
  - **Poor PS, declined GFR, elderly: Carboplatin-doublets, or single agent**
- **Second-line treatment (Cisplatin-resistant)**
  - **Gemcitabine, paclitaxel, docetaxel, ifosfamide, nab-paclitaxel, vinflunine, and pemetrexed.**

New agents

- Immune Modulation (Tumor Vaccines)
- Pemetrexed (Sweeney, 2006 JCO)
- Trastuzumab (Hussain, 2007 JCO; Single-agent CALGB study)
- Gefitinib (Galsky, 2007 Invest New Drugs; Philips, 2009 Ann Oncol)
- Erlotinib (Ongoing studies)
- Sorafenib (Sridhar, 2008 ASCO GU, #340)
- Sunitinib (Gallagher, 2007 ASCO, #5080; Bellmunt, 2008 ASCO GU, #291)
- Bevacizumab (With GC: Ongoing CALGB study; Hahn, 2009 ASCO, #5018)
- Vinflunine (Vaughn, 2008 ASCO GU, #316)
- FGFR3 Inhibitors (Ongoing studies)
- Histone Deacetylase Inhibitors (Vorinostat, AR42)

Muscle-Invasive Disease

Treatment decision-making!

- Who needs cystectomy?
- Who can be cured with bladder preservation?
- Who needs multimodality treatment (neoadjuvant/adjuvant treatments)?

Surgical treatment outcome

- In the U.S., the Gold Standard Treatment of muscle-invasive disease is radical cystectomy with bilateral pelvic lymph node dissection.
- After surgery, 40-50% of these patients develop metastases within 2-5 years and most die of their disease.

How to improve outcome?

- **Bladder cancer is a radio- and chemo-sensitive disease.**
- **Cisplatin-based chemotherapies have 40-75% RRs with 12-20% CRs.**
- **Multimodality treatment with neoadjuvant/adjuvant chemotherapy and/or radiation therapy can potentially improve outcome.**

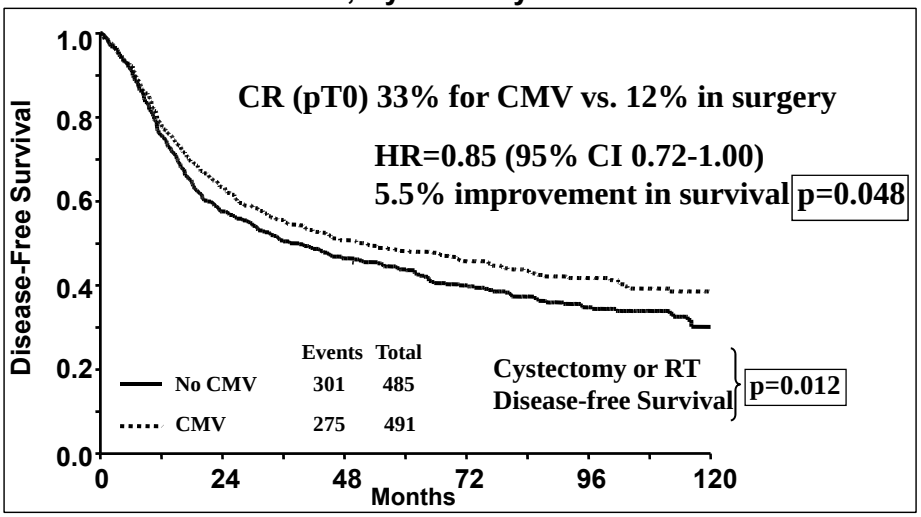
Randomized Neoadjuvant Trials

Study	Neoadjuvant Arm	Standard Arm	Patients (N)	Survival
Cisplatin chemotherapy				
Australia/UK[17]	Cis/RT	RT	255	No difference
Canada/NCI[18]	Cis/RT or preop RT+cystectomy	RT or preop RT+cystectomy	99	No difference
Spain (CUETO)[19]	Cis/cystectomy	Cystectomy	121	No difference
Combination chemotherapy				
EORTC/MRC[11]	CMV/RT or cystectomy	RT or cystectomy	976	5.5% difference in favor of CMV
SWOG Intergroup[20]	M-VAC/cystectomy	Cystectomy	298	Benefit with M-VAC ($P = 0.06$)
Italy (GUONE)[15]	M-VAC/cystectomy	Cystectomy	206	No difference
Italy (GISTV)[21]	M-VEC/cystectomy	Cystectomy	171	No difference
Genoa[22]	Cis/5-FU/RT/cystectomy	Cystectomy	104	No difference
Nordic I[24]	ADM/Cis/RT/cystectomy	RT/cystectomy	311	No difference, 15% benefit with ADM + Cis in T3–T4a
Nordic II[16]	MTX/Cis/cystectomy	Cystectomy	317	No difference
Abol-Enein *et al.*[23]	CarboMV/cystectomy	Cystectomy	194	Benefit with CarboMV

Sternberg *Urology* 2007

EORTC/MRC Trial

* 976 pts, 106 centers in 20 countries, f/u 7 yrs
* CMV: 491 pts; Control: 485 pts
* Management of primary per treating MD:
  - RT, Cystectomy or both

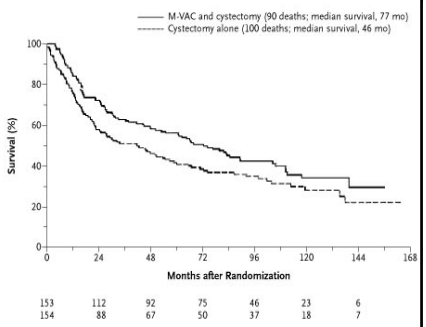


Hall *Lancet* 1999

SWOG Intergroup

* 307 pts, 1987-1998; 126 centers in the U.S., f/u 8.7 yrs
* MVAC + Surgery: 153 pts, Surgery: 154 pts
* Management of primary: Radical Cystectomy

	MVAC	Surgery	P-value
Median Survival	77 mos	46 mos	0.05
5yr Survival	57%	43%	0.06
pT0	38%	15%	<0.001
Death HR	1.33 (33% reduction in mortality)		
Disease-specific HR	1.66		0.002



Grossman *NEJM* 2003

Meta-analysis Studies

NEOADJUVANT CHEMOTHERAPY FOR TRANSITIONAL CELL CARCINOMA OF THE BLADDER: A SYSTEMATIC REVIEW AND META-ANALYSIS

ERIC WINQUIST,*† TRICIA S. KIRCHNER, ROANNE SEGAL, JOSEPH CHIN‡ AND HIMU LUKKA§ ON BEHALF OF THE GENITOURINARY CANCER DISEASE SITE GROUP OF CANCER CARE ONTARIO PROGRAM IN EVIDENCE-BASED CARE PRACTICE GUIDELINES INITIATIVE‖

Winquist E, et al. *J Urol* 171:561, 2004

- **8 randomized trials with cisplatin-based combination chemotherapy**
  - **HR for death 0.87 (p=0.006) and 6.5% absolute improvement in five-year OS (50% to 56.5%).**

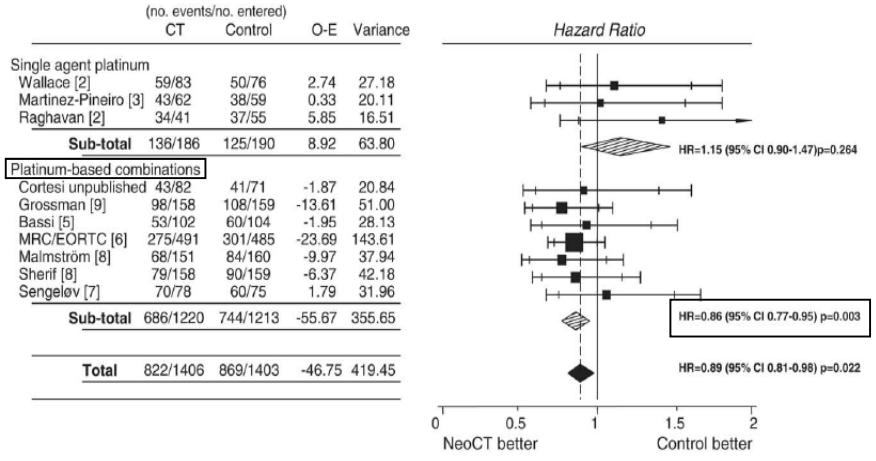
Meta-analysis Studies

Neoadjuvant Chemotherapy in Invasive Bladder Cancer: Update of a Systematic Review and Meta-Analysis of Individual Patient Data

Advanced Bladder Cancer (ABC) Meta-analysis Collaboration ***Eur Urol* 48:202, 2005**

Meta-analysis Group, Medical Research Council Clinical Trials Unit, 222 Euston Road, London NW1 2DA, UK

- **11 randomized trials, 3005 pts**



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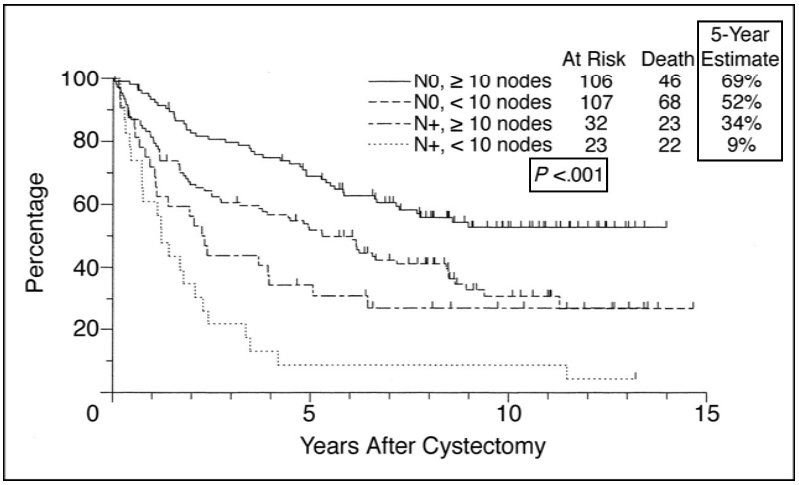
- 11 randomized trials, 3005 pts

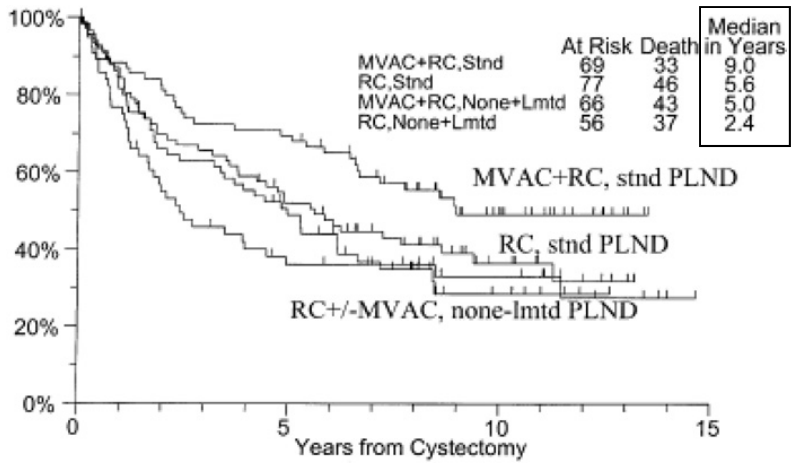
- **Overall survival benefit:**
  - **14% reduction in the risk of death (HR=0.86, p=0.003)**
  - **5% (45% to 50%) at 5 years**
- **Disease-free survival benefit:**
  - **22% reduction in the risk of recurrence (HR=0.78, p<0.0001)**
  - **9% absolute improvement at 5 years**

The impact of surgical factors



Herr, et al. *JCO* 22:2781, 2004

The impact of optimal combined modality treatment: Analysis of INT-0080



Herr, et al. *Journal of Urology 177*:437, 2007

Summary

- The quality of radical cystectomy and the extent of pelvic lymph node dissection have a major impact on invasive bladder cancer survival*
- Radical surgery alone does not provide long-term survival for about half of the patients with invasive bladder cancer

*Elting LS, et al. *Cancer 104*:975, 2005
*Joudi Fn, et al. *Journal of Urology 174*:432, 2005

Summary

- **Adjuvant cisplatin-based chemotherapy (~4 cycles) can be offered to high-risk patients (>T2) and it improves disease-free survival and prevent recurrence, but its benefit for overall survival, yet to be determined (level 2)**

Summary

- **Neoadjuvant cisplatin-based combination chemotherapy can be delivered safely, significantly improves P0 rate (no evidence of cancer at cystectomy), and disease-free and overall survivals (level 1 evidence)**

In Conclusion

- **Patients with muscle-invasive bladder cancer require multimodality care and the optimal curative strategy for most of them is neoadjuvant cisplatin-based combination chemotherapy followed by radical cystectomy and complete pelvic lymph node dissection**