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*

<table>
<thead>
<tr>
<th>Gender</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>848,170</td>
</tr>
<tr>
<td>Women</td>
<td>790,740</td>
</tr>
</tbody>
</table>

- Prostate
- Lung & bronchus
- Colon & rectum
- Urinary bladder
- Melanoma of the skin
- Kidney & renal pelvis
- Non-Hodgkin lymphoma
- Oral cavity & pharynx
- Leukemia
- Pancreas
- All Other Sites

Breast
- Lung & bronchus
- Colon & rectum
- Uterine corpus
- Thyroid
- Melanoma of the skin
- Non-Hodgkin lymphoma
- Kidney and renal pelvis
- Ovary
- Pancreas
- 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

<table>
<thead>
<tr>
<th>Gender</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>301,820</td>
</tr>
<tr>
<td>Women</td>
<td>275,370</td>
</tr>
</tbody>
</table>

- Lung & bronchus
- Prostate
- Colon & rectum
- Pancreas
- Liver & intrahepatic bile duct
- Leukemia
- Esophagus
- Urinary bladder
- Non-Hodgkin Lymphoma
- Kidney & Renal Pelvis
- All other sites

- Lung & bronchus
- Breast
- Colon & rectum
- Pancreas
- Ovary
- Leukemia
- Non-Hodgkin lymphoma
- Uterine corpus
- Liver & intrahepatic bile ducts
- Brain & other nervous system
- 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\textsuperscript{th}-7\textsuperscript{th} decades)
  - Rising incidence (20\% over the last 20-yr)

Epidemiology

- In U.S., the second most prevalent cancer in men\geq60
- Bladder cancer has significant financial impact on healthcare
  - Requires intensive, life-long cystoscopic, radiologic, and cytologic surveillance
  - Most expensive malignancy in the U.S.\,*

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

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transitional Cell Carcinoma</td>
<td>90-95%</td>
</tr>
<tr>
<td>Squamous Cell Carcinoma</td>
<td>3%</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>2%</td>
</tr>
<tr>
<td>Small Cell Carcinoma</td>
<td>1%</td>
</tr>
<tr>
<td>Others</td>
<td>1%</td>
</tr>
</tbody>
</table>

### 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**
  - Transurethral 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.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Ta, Tis</td>
</tr>
<tr>
<td>I</td>
<td>T1 only</td>
</tr>
<tr>
<td>II</td>
<td>T2a, T2b</td>
</tr>
<tr>
<td>III</td>
<td>T3a, T3b (perivesical tumor) T4a (prostate, uterus or vagina)</td>
</tr>
<tr>
<td>IV</td>
<td>T4b (pelvic or abdominal wall) Any N or M</td>
</tr>
</tbody>
</table>

## Stages at Presentation

- 75% Superficial cancer
- 20% Muscle-invasive cancer
- 5% Metastatic disease
### Bladder Cancer Stage: Prognosis

<table>
<thead>
<tr>
<th>Location</th>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
<th>Survival (5 yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superficial</td>
<td>0a</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
<td>&gt; 80%</td>
</tr>
<tr>
<td>Supra muscular</td>
<td>I</td>
<td>T1a</td>
<td>N0</td>
<td>M0</td>
<td>80-90%</td>
</tr>
<tr>
<td>Lamina</td>
<td>I</td>
<td>T2b</td>
<td>N0</td>
<td>M0</td>
<td>30-40%</td>
</tr>
<tr>
<td>Early muscle</td>
<td>II</td>
<td>T2a</td>
<td>N0</td>
<td>M0</td>
<td>30-40%</td>
</tr>
<tr>
<td>Deep muscle</td>
<td>II</td>
<td>T2b</td>
<td>N0</td>
<td>M0</td>
<td>20-40%</td>
</tr>
<tr>
<td>Perivesical Fat</td>
<td>III</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
<td>15-25%</td>
</tr>
<tr>
<td>Lymph Nodes</td>
<td>IV</td>
<td>Any T</td>
<td>N1-3</td>
<td>M0</td>
<td>5-20%</td>
</tr>
<tr>
<td>Metastatic</td>
<td>IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
<td>&lt; 2%</td>
</tr>
</tbody>
</table>

AJCC Cancer Staging, 1998

### Natural History of Bladder Cancer

- Bladder cancer diagnosed
  - 60%
  - 20%
    - Non-invasive (Ta and T1)
      - 50%
      - 50%
        - No invasion
          - 50%–70%
        - ≥1 invasion
          - 20%–40%
          - Superficial invasive disease
            - Good prognosis
          - Progression to muscle-invasive disease
            - Poor prognosis

Colquhoun AJ, et al.  
Postgrad Med J. 2002
Superficial Bladder Cancer

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Department of Urology
The James Cancer Hospital and
The Ohio State University Wexner Medical Center

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**

<table>
<thead>
<tr>
<th>Primary Tumor (T)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Ta</td>
<td>Noninvasive papillary carcinoma</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ: “flat tumor”</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor invades subepithelial connective tissue</td>
</tr>
</tbody>
</table>

- **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

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# Papillary Bladder Tumors

![Image of papillary bladder tumors](image1.png) ![Image of papillary bladder tumors](image2.png)
**Flat Bladder Tumors (Carcinoma in situ (CIS))**

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

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**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

<table>
<thead>
<tr>
<th>% Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>90</td>
</tr>
<tr>
<td>59</td>
</tr>
<tr>
<td>71</td>
</tr>
<tr>
<td>55</td>
</tr>
<tr>
<td>40</td>
</tr>
<tr>
<td>95</td>
</tr>
<tr>
<td>73</td>
</tr>
<tr>
<td>60</td>
</tr>
<tr>
<td>72</td>
</tr>
<tr>
<td>90</td>
</tr>
<tr>
<td>88</td>
</tr>
<tr>
<td>74</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>% Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
</tr>
<tr>
<td>18</td>
</tr>
<tr>
<td>2.4</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>7</td>
</tr>
<tr>
<td>39</td>
</tr>
<tr>
<td>16</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>25</td>
</tr>
<tr>
<td>52</td>
</tr>
<tr>
<td>39</td>
</tr>
<tr>
<td>30</td>
</tr>
</tbody>
</table>
### 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**


European Urology 49:466, 2006

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### Recurrence and Progression

**Superficial Bladder Cancer**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Recurrence</th>
<th>Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of tumors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2 to 7</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>≥8</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Tumor size</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</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>&lt;1 rec/yr</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>&gt;1 rec/yr</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>T 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>

European Urology 49:466, 2006
## Recurrence and Progression in Superficial Bladder Cancer

<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>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 (59-62)</td>
<td>78 (72-84)</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>2-6</td>
<td>1 (0.4-1.8)</td>
<td>6 (3-8)</td>
<td>Low risk</td>
</tr>
<tr>
<td>7-13</td>
<td>5 (4-7)</td>
<td>17 (14-20)</td>
<td>Intermediate 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.

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. Cauberga, Daniël M. de Bruinia, Dirk J. Fabera, Tom G. van Leeuwenb, Jean J.M.C.H. de la Rosetec, Theoc M. de Reijkea

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

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

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

• 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 into 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

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

<table>
<thead>
<tr>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk</td>
</tr>
<tr>
<td>Intermediate Risk</td>
</tr>
<tr>
<td>High Risk</td>
</tr>
</tbody>
</table>

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**

![Office Cystoscopy Image](image)

### 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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Assistant Professor
Department of Internal Medicine
Division of Medical Oncology
The Ohio State University Wexner Medical Center
## 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%)

<table>
<thead>
<tr>
<th># of PF</th>
<th>MS (mo)</th>
<th>CR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>33</td>
<td>35</td>
</tr>
<tr>
<td>1</td>
<td>13.4</td>
<td>11</td>
</tr>
<tr>
<td>2</td>
<td>9.3</td>
<td>0</td>
</tr>
</tbody>
</table>

\[ p = 0.0001 \]  
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.

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(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

<table>
<thead>
<tr>
<th></th>
<th>GC</th>
<th>MVAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia (Grade 3/4)</td>
<td>71%</td>
<td>82%</td>
</tr>
<tr>
<td>Neutropenic sepsis</td>
<td>1%</td>
<td>12%</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>1.5%</td>
<td>13.4%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>57%</td>
<td>21%</td>
</tr>
<tr>
<td>Mucositis</td>
<td>1%</td>
<td>22%</td>
</tr>
<tr>
<td>Alopecia</td>
<td>11%</td>
<td>55%</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>22%</td>
<td>21%</td>
</tr>
<tr>
<td>Drug-toxicity death rate</td>
<td>1%</td>
<td>3%</td>
</tr>
</tbody>
</table>
GC vs. MVAC
Response and Survival

<table>
<thead>
<tr>
<th></th>
<th>GC (203)</th>
<th>MVAC (202)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR</td>
<td>49.4%</td>
<td>45.7%</td>
</tr>
<tr>
<td></td>
<td>CR 12.2%</td>
<td>11.9%</td>
</tr>
<tr>
<td></td>
<td>PR 37.2%</td>
<td>33.8%</td>
</tr>
<tr>
<td>MS</td>
<td>13.8</td>
<td>14.8</td>
</tr>
<tr>
<td></td>
<td>(12.3-15.8)</td>
<td>(13.2-16.8)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Neoadjuvant Arm</th>
<th>Standard Arm</th>
<th>Patients (N)</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cisplatin chemotherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Australia/UK17</td>
<td>Cis/RT</td>
<td>RT</td>
<td>265</td>
<td>No difference</td>
</tr>
<tr>
<td>Canada/NU18</td>
<td>Cis/Hi or preop</td>
<td>Hi or preop</td>
<td>1/1</td>
<td>No difference</td>
</tr>
<tr>
<td>Spain (CHETO)19</td>
<td>Cis/cystectomy</td>
<td>Cystectomy</td>
<td>121</td>
<td>No difference</td>
</tr>
<tr>
<td><strong>Combination chemotherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FORRC/MRSS11</td>
<td>CMV/RT or cystectomy</td>
<td>RT or cystectomy</td>
<td>678</td>
<td>5.5% difference in favor of CMV Benefit with M-VAC</td>
</tr>
<tr>
<td>SWOG intergroup20</td>
<td>MVAC/cystectomy</td>
<td>Cystectomy</td>
<td>268</td>
<td>(P = 0.06)</td>
</tr>
<tr>
<td>Italy (CUONE)16</td>
<td>MVAC/cystectomy</td>
<td>Cystectomy</td>
<td>206</td>
<td>No difference</td>
</tr>
<tr>
<td>Italy (GISTV)12</td>
<td>MVEC/cystectomy</td>
<td>Cystectomy</td>
<td>171</td>
<td>No difference</td>
</tr>
<tr>
<td>Genova22</td>
<td>Cis/5FU/RT/cystectomy</td>
<td>Cystectomy</td>
<td>104</td>
<td>No difference</td>
</tr>
<tr>
<td>Nordic I24</td>
<td>ADM/Cis/RT/cystectomy</td>
<td>RT/cystectomy</td>
<td>311</td>
<td>No difference, 15% benefit with ADM = Cis in T3-T4a</td>
</tr>
<tr>
<td>Nordic II56</td>
<td>Mtx/Cis/cystectomy</td>
<td>Cystectomy</td>
<td>317</td>
<td>No difference</td>
</tr>
<tr>
<td>Abol Esmail et al.23</td>
<td>CarbMoV/cystectomy</td>
<td>Cystectomy</td>
<td>194</td>
<td>Benefit with CarbMoV</td>
</tr>
</tbody>
</table>

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

CR (pT0) 33% for CMV vs. 12% in surgery

\[ HR = 0.85 \ (95\% \ CI \ 0.72-1.00) \]

5.5% improvement in survival \( p = 0.048 \)

**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

<table>
<thead>
<tr>
<th></th>
<th>MVAC</th>
<th>Surgery</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Survival</td>
<td>77 mos</td>
<td>46 mos</td>
<td>0.05</td>
</tr>
<tr>
<td>5yr Survival</td>
<td>57%</td>
<td>43%</td>
<td>0.06</td>
</tr>
<tr>
<td>pT0</td>
<td>38%</td>
<td>15%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death HR</td>
<td>1.33</td>
<td>(33% reduction in mortality)</td>
<td></td>
</tr>
<tr>
<td>Disease-specific HR</td>
<td>1.66</td>
<td>0.002</td>
<td></td>
</tr>
</tbody>
</table>

**Hall Lancet 1999**

**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. KIRKNESS, ROANNE SEGAL, JOSEPH CHING AND HEDU LUKKA

(ADAPTED FROM THE ONTARIO PROSTATE CANCER OUTCOMES PROGRAM IN EVIDENCE-BASED CARE PRACTICE GUIDELINES INITIATIVE)


• 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


• 11 randomized trials, 3005 pts

<table>
<thead>
<tr>
<th></th>
<th>CT</th>
<th>Control</th>
<th>O/E</th>
<th>Variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single agent platinum</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wollin [2]</td>
<td>59/83</td>
<td>50/76</td>
<td>2.74</td>
<td>27.18</td>
</tr>
<tr>
<td>Martinez-Pinero [3]</td>
<td>43/62</td>
<td>38/58</td>
<td>0.33</td>
<td>20.11</td>
</tr>
<tr>
<td>Raghavan [2]</td>
<td>34/41</td>
<td>37/52</td>
<td>0.85</td>
<td>16.51</td>
</tr>
<tr>
<td>Sub-total</td>
<td>136/186</td>
<td>125/100</td>
<td>8.92</td>
<td>63.80</td>
</tr>
</tbody>
</table>

Platinum-based combinations

<table>
<thead>
<tr>
<th></th>
<th>CT</th>
<th>Control</th>
<th>O/E</th>
<th>Variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin, unpublished</td>
<td>43/82</td>
<td>41/71</td>
<td>-1.87</td>
<td>20.84</td>
</tr>
<tr>
<td>Maimon [8]</td>
<td>88/151</td>
<td>84/160</td>
<td>-9.97</td>
<td>37.94</td>
</tr>
<tr>
<td>Shariat [6]</td>
<td>76/156</td>
<td>90/159</td>
<td>-6.37</td>
<td>42.18</td>
</tr>
<tr>
<td>Sengupta [7]</td>
<td>70/78</td>
<td>60/72</td>
<td>-1.79</td>
<td>31.96</td>
</tr>
<tr>
<td>Sub-total</td>
<td>696/1220</td>
<td>744/1213</td>
<td>-55.67</td>
<td>355.65</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>622/1406</td>
<td>866/1403</td>
<td>-46.75</td>
<td>419.45</td>
</tr>
</tbody>
</table>
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

- 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

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

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.