Overview of Bladder Cancer

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Medical Oncology Branch
Center for Cancer Research
National Cancer Institute
National Institutes of Health
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Epidemiology

- 4th most common malignancy in men and the 9th most common in women
- Estimated 70,530 new cases and 14,680 deaths in the year 2010
- Median age is 68 years
- 90% over age 55, > 50% over age 73
- 3:1 male to female ratio
Risk Factors

- Smoking: accounts 50% in US, 3-5 folds higher risk in smokers.
- Aromatic amines, certain occupations: leather/rubber/painting (analine dyes, vinyl, etc)
- Prior pelvic irradiation
- Prior cyclophosphamide
- Schistosomiasis (squamous cell carcinoma and TCC)
- Chronic cystitis (squamous cell ca)
- HNPCC (with upper tract tumors)
Molecular Genetics

- No specific genetic abnormality that is diagnostic of bladder cancer
- Involved in tumorogenesis:
  - p53 mutations
  - Rb
  - deletions on chromosome 9
  - overexpression of c-erb-B2
  - H-ras mutations
## Histology

<table>
<thead>
<tr>
<th>Type of Carcinoma</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transitional Cell Carcinoma</td>
<td>90%</td>
</tr>
<tr>
<td>Squamous Cell Carcinoma</td>
<td>5%</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>0.5-2%</td>
</tr>
<tr>
<td>Small Cell Carcinoma</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

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Urothelial Carcinoma

Transitional Cell Carcinoma
Includes:
- Bladder
- Ureter
- Renal pelvis (5-10% of all renal tumors)

Have a similar natural history and similar management principles may be applied to each.
Staging

*T4a – invades prostate, uterus, vagina
*T4b – invades pelvic wall, abdominal wall
## Staging

<table>
<thead>
<tr>
<th></th>
<th>T1</th>
<th>T2ab</th>
<th>T3ab</th>
<th>T4ab</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>I</td>
<td>IIA</td>
<td>IIIA</td>
<td>IIIB</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IIB</td>
<td></td>
<td>IV</td>
</tr>
<tr>
<td>N123</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
</tr>
<tr>
<td>M1</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
</tr>
</tbody>
</table>

N1 – single LN < 2cm  
N2 – single LN > 2cm - 5cm; or multiple LNs, none > 5cm  
N3 – LN(s) > 5cm

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Clinical presentation

- Painless gross hematuria 80%
- Irritative symptoms 20%: urinary frequency, urgency and dysuria, suggesting Cis and muscle invasive dx.
- Some asymptomatic: microscopic hematuria.
- Advanced dx: urinary obstruction or involved organ symptoms.
Workup and Diagnosis

- Urinalysis, urine cytology (sensitivity 40-60%) and cystoscopy
- CT scan (with contrast) to establish patency of urinary tract and to assess pelvic and RP LNs
- CT chest with locally advanced disease
- Bone scan if complaints c/w osseous metastases
- PET/CT is currently being investigated
Cystoscopic Evaluation

Transurethral resection (TUR) of the bladder is a surgical procedure that is used both to diagnose bladder cancer and to remove cancerous tissue from the bladder.
Transurethral Resection of Bladder Tumor
Superficial Bladder Cancer

- TURBT +/- Intravesical Therapy

Invasive Bladder Cancer

- Neoadjuvant cisplatin combination chemotherapy
- Clinical trial: Non-cisplatin based neoadjuvant chemotherapy
- Trimodality Bladder Sparing Protocol

Metastatic Bladder Cancer

- Cisplatin based chemotherapy
- Clinical Trial: Non-cisplatin based chemotherapy

Radical Cystectomy
Treatment Options for Superficial Bladder Cancer

- Transurethral resection
- Cystectomy
- Laser treatment
- Photodynamic therapy
- Intravesical therapy
  - Chemotherapy
  - BCG
  - Interferon
  - BCG + interferon
Primary Superficial Bladder Cancer Risk Groups
Stratified by Tumor Grade and Stage

Low Risk
- Grade I, stage Ta disease
- Single grade I, stage T1 tumor
Recurrence 37%, progression 0%, mortality 0%

Intermediate Risk
- Multiple grade I, stage T1 tumors
- Grade II, stage Ta disease
- Single grade II, stage T1 tumor
Recurrence 45%, progression 1.8%, mortality 0.73%

High Risk
- Multiple grade II, stage T1 tumors
- Grade III, stage Ta or T1 disease
- Carcinoma in situ
Recurrence 54%, progression 15%, mortality 9.5%

Intravesical Therapy

**Indications**

- Multiple tumor recurrences or rapidly recurrent disease
- Large (>5 cm) solid bladder tumor
- Lamina propria invasion
- Multifocal disease
- High-grade Ta disease or any grade T1 disease
- Carcinoma in situ
- Extravesical involvement (prostatic urethra)
- Postresection positive cytology (after negative workup of upper urinary tracts)
### BCG Is More Effective Than Chemotherapy for Reducing Rate of Recurrence and Progression

<table>
<thead>
<tr>
<th>Agent</th>
<th>Patients/ series/sig</th>
<th>Recurrence (%)</th>
<th>Progression (%)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Ctrl</td>
<td>Rx</td>
<td>Benefit</td>
</tr>
<tr>
<td>Thiotepa</td>
<td>1007/10/6</td>
<td>56</td>
<td>44</td>
<td>12</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>1241/5/3</td>
<td>47</td>
<td>34</td>
<td>13</td>
</tr>
<tr>
<td>Mytomycin C</td>
<td>1157/6/2</td>
<td>50</td>
<td>35</td>
<td>15</td>
</tr>
<tr>
<td>BCG</td>
<td>496/5/4</td>
<td>72</td>
<td>32</td>
<td>40</td>
</tr>
</tbody>
</table>

Series = Number of controlled studies; sig = Number of controlled studies statistically significant ($P < .05$), as reported by the authors. NS = not significant.

Lamm DL. *Eur Urol.* 1995;27(suppl 1):2. Reprinted with permission from S Karger AG.
Maintenance Therapy Improves Outcomes

**SWOG Study**

- N = 384 disease free after induction BCG (Connaught strain)
- Maintenance: full dose for 3 weeks at 3 and 6 months, then q6mo for 3 years

**Recurrence-Free Survival**

- Survival data with statistical significance: $P < .0001$

**Progression-Free Survival**

- Survival data with statistical significance: $P = .04$

**Survival**

- Survival data with statistical significance: $P = .08$

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Muscle-invasive BC

- Radical cystectomy with bilateral LND, standard in US, mortality ~5%.
- Over 90% local control.
- Very high metastatic potential, 50% develop metastatic dx in 2 yrs.
- Most important prognostic factor for survival is pathologic stage.
USC/Norris Bladder Cancer Experience in 1054 Patients

Probability of Survival According to Pathologic Groups

- Organ Confined (n=594)
- Extravesical (n=214)
- Lymph Node (+) (n=246)

$P < 0.001$

J Clin Oncol 2001;19:666

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Muscle Invasive Disease

- Radical cystectomy (includes bladder, regional pelvic LNs, distal ureters)
  - in men, prostate gland, seminal vesicles, and proximal urethra are included
  - in women, the urethra, uterus, fallopian tubes, anterior vaginal wall and surrounding fascia are included
Urinary Diversion

- Ileal conduit
- Continent cutaneous reservoir
- Orthotopic urethral diversions (neobladder)
An isolated segment of the ileum is exteriorized in the form of a stoma through the abdominal wall with an appliance secured for continuous drain of urine.
Continent cutaneous reservoirs

- A pouch is made of detubularized bowel for urinary storage
- A tapered bowel segments connects to skin
- Requires intermittent clean self catherization
Orthotopic urethral diversions (neobladder)

- Spherical pouch is made from detubularized bowel for urinary storage
- Ureters are anastomized to the pouch which is then anastomosed to native urethra
FAQ’s on Muscle-Invasive Bladder Cancer

- Is there a benefit to neoadjuvant chemotherapy?
- Is there a benefit to adjuvant chemotherapy?
- What should be the standard of care?
- What about GC vs MVAC as neoadjuvant or adjuvant chemotherapy?
Potential impact of postoperative early complications on the timing of adjuvant chemotherapy in patients undergoing radical cystectomy

Complications within 90 days of surgery using a 5-grade system.

- **Grade 1:** oral medication/bedside care
- **Grade 2:** IV therapy, transfusion, hyperalimentation, enteral feedings
- **Grade 3:** intubation, interventional radiology, or re-operative intervention
- **Grade 4:** organ resection or chronic disability
- **Grade 5:** death

- 30% of pts experienced a grade 2-5 complication potentially interfere with the administration of adjuvant chemotherapy

### All Complications Grades 2-5

<table>
<thead>
<tr>
<th>Complication Category</th>
<th>0-30 days post RC</th>
<th>30-60 days post RC</th>
<th>60-90 days post RC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=611 pts (%)</td>
<td>N=547 pts (%)</td>
<td>N=97 pts (%)</td>
</tr>
<tr>
<td>GI 242 (40%)</td>
<td>GI 214 (39%)</td>
<td>GI 53 (55%)</td>
<td>GI 28 (52%)</td>
</tr>
<tr>
<td>Infection 240 (39%)</td>
<td>Infection 175 (32%)</td>
<td>GU 22 (23%)</td>
<td>GI 16 (30%)</td>
</tr>
<tr>
<td>Cardiac 115 (19%)</td>
<td>Cardiac 103 (19%)</td>
<td>GI 19 (20%)</td>
<td>GU 8 (15%)</td>
</tr>
<tr>
<td>Bleeding 99 (16%)</td>
<td>Bleeding 90 (16%)</td>
<td>DVT/PE 14 (14%)</td>
<td>Wound 6 (11%)</td>
</tr>
<tr>
<td>DVT/PE 92 (15%)</td>
<td>DVT/PE 76 (14%)</td>
<td>Wound 12 (12%)</td>
<td>Bleeding 4 (7%)</td>
</tr>
<tr>
<td>Wound 88 (14%)</td>
<td>Wound 71 (13%)</td>
<td>Cardiac 12 (12%)</td>
<td>DVT/PE 3 (6%)</td>
</tr>
<tr>
<td>GU 85 (14%)</td>
<td>Pulmonary 63 (12%)</td>
<td>Pulmonary 5 (5%)</td>
<td>Pulmonary 2 (4%)</td>
</tr>
<tr>
<td>Pulmonary 68 (11%)</td>
<td>GU 59 (11%)</td>
<td>Neurologic 5 (5%)</td>
<td>Neurologic 2 (4%)</td>
</tr>
<tr>
<td>Neurologic 29 (5%)</td>
<td>Neurologic 21 (4%)</td>
<td>Bleeding 5 (5%)</td>
<td>Misc 2 (4%)</td>
</tr>
<tr>
<td>Misc 13 (2%)</td>
<td>Misc 9 (2%)</td>
<td>Misc 2 (2%)</td>
<td>Surgical 1 (2%)</td>
</tr>
<tr>
<td>Surgical 7 (1%)</td>
<td>Surgical 6 (1%)</td>
<td>Surgical 0 (0%)</td>
<td>Cardiac 1 (2%)</td>
</tr>
</tbody>
</table>
## Randomized Trials of Adjuvant Therapy

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Chemotherapy</th>
<th>No.Pts</th>
<th>Survival benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skinner</td>
<td>1991</td>
<td>cisplatin, cyclophosphamide, and doxorubicin</td>
<td>102</td>
<td>Yes</td>
</tr>
<tr>
<td>Studer</td>
<td>1994</td>
<td>cisplatin</td>
<td>77</td>
<td>No</td>
</tr>
<tr>
<td>Stockle</td>
<td>1995</td>
<td>cisplatin, methotrexate, vinblastine, doxorubicin or epirubicin</td>
<td>49</td>
<td>Yes</td>
</tr>
<tr>
<td>Freiha</td>
<td>1996</td>
<td>cisplatin, methotrexate, vinblastine</td>
<td>55</td>
<td>No</td>
</tr>
<tr>
<td>Bono</td>
<td>1997</td>
<td>cisplatin, methotrexate</td>
<td>93</td>
<td>No</td>
</tr>
<tr>
<td>Otto</td>
<td>2001</td>
<td>cisplatin, methotrexate, vinblastine, epirubicin</td>
<td>108</td>
<td>No</td>
</tr>
</tbody>
</table>
Randomized Trials of Adjuvant Therapy

- Hampered by serious methodological flaws
- Major deficiencies observed:
  - small sample size
  - early stopping of patient entry
  - statistical analyses
  - pts in chemo group that did not receive Rx were moved to non-chemo group for analysis
  - pts who relapsed did not routinely receive chemotherapy
The power of this meta-analysis is clearly limited.
Arm I: GC randomized to 1 of 2 schedules.

- **GC2**: cisplatin on day 2 and gemcitabine on days 1, 8, and 15.
- **GC15**: cisplatin on day 15 and gemcitabine on days 1, 8, 15.

Arm II: Patients undergo observation followed by GC at relapse.

194 patients randomized

Design: 610 patients to detect 10% difference in 5 yr survival.
Treatment in both regimens repeats every 28 days for 4 courses.
(T2 [G3 only] or T3-4 [any G], N0-2 vs any T, N1-2, M0).
Cognetti et al. Adjuvant gemcitabine and cisplatin in patients with muscle-invasive bladder cancer

Overall Survival

$\text{CG B2}$

$\text{CG B15}$

$\text{control}$

$p=0.25$
Paz-Ares et al. ASCO 2010: Randomized phase III trial comparing adjuvant paclitaxel/gemcitabine/cisplatin (PGC) to observation in patients with resected invasive bladder cancer: SOGUG 99/01 study

Eligibility
- TCC
- Post-cystectomy
- pT3-4 and/or pN+
- PS 0-1
- CrCl > 50ml/min

142 patients randomized

PGC x4

Observation

N=340 to detect 15% increase
In 2 years OS (50% -> 65%)
Alpha 0.05 and beta 0.2

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Overall Survival - ITT

HR: 0.44 ; P< 0.0009
HR: 0.378 ( 95% CI: 0.649-0.221) P<0.0004 Adjusted - Cox Multivariate
## Treatment at Relapse

<table>
<thead>
<tr>
<th></th>
<th>PGC N=30</th>
<th>Observation N=54</th>
</tr>
</thead>
<tbody>
<tr>
<td>Further Chemo</td>
<td>16 (53%)</td>
<td>38 (70%)</td>
</tr>
<tr>
<td>Platinum-based</td>
<td>13 (43%)</td>
<td>33 (61%)</td>
</tr>
<tr>
<td>Non-platinum-based</td>
<td>3 (10%)</td>
<td>5 (9%)</td>
</tr>
</tbody>
</table>

Paz-Ares et al. ASCO 2010
EORTC Early vs Delayed Chemotherapy after Cystectomy pT3-pT4, and/or N+M0

Randomize

Gem-Cis x 4 or
M-VAC x 4 or
HD-M-VAC x 4

Therapy at relapse

Increase in 5 yr survival from 35 to 42%. (7% increase)
Alpha .05; Beta .20:
644 pts closed June 2008 298 accrued

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### Randomized Trials of Adjuvant Therapy

<table>
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<tr>
<td>Otto</td>
<td>2001</td>
<td>cisplatin, methotrexate, vinblastine, epirubicin</td>
<td>108</td>
<td>No</td>
</tr>
<tr>
<td>Cognetti</td>
<td>2008</td>
<td>cisplatin, gemcitabine</td>
<td>192</td>
<td>No</td>
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<tr>
<td>Stadler</td>
<td>2009</td>
<td>cisplatin, methotrexate, vinblastine, doxorubicin</td>
<td>114</td>
<td>No</td>
</tr>
<tr>
<td>Paz-Ares</td>
<td>2010</td>
<td>cisplatin, paclitaxel, gemcitabine</td>
<td>142</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Adjuvant Chemotherapy

• Meta-analyses need to be updated to include these large randomized trials

• Insufficient evidence to support the routine use of adjuvant chemotherapy

• All patients should be informed about neoadjuvant chemotherapy benefits derived from data on over 3000 randomized patients on 12 randomized trials

• If the patient refuses, then adjuvant chemotherapy should be considered but the data are less compelling
### What are the Neoadjuvant Chemotherapy Data?

<table>
<thead>
<tr>
<th>Series</th>
<th>ChemoRx</th>
<th>Pts</th>
<th>Primary Rx</th>
<th>Survival Benefit</th>
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</thead>
<tbody>
<tr>
<td>Shearer</td>
<td>MTX</td>
<td>376</td>
<td>RT/cyst</td>
<td>No</td>
</tr>
<tr>
<td>Wallace</td>
<td>Cisplatin</td>
<td>225</td>
<td>RT</td>
<td>No</td>
</tr>
<tr>
<td>Martinez-Piniero</td>
<td>Cisplatin</td>
<td>121</td>
<td>Cyst</td>
<td>No</td>
</tr>
<tr>
<td>Nordic-2</td>
<td>MTX-Cisplatin</td>
<td>317</td>
<td>Cyst</td>
<td>No</td>
</tr>
<tr>
<td>Vitale</td>
<td>Cis/FU/RT</td>
<td>104</td>
<td>Cyst</td>
<td>No</td>
</tr>
<tr>
<td>Shipley</td>
<td>CMV</td>
<td>121</td>
<td>Cisplatin-RT</td>
<td>No</td>
</tr>
<tr>
<td>Pellegrini</td>
<td>MVEC</td>
<td>171</td>
<td>Cyst</td>
<td>No</td>
</tr>
<tr>
<td>Malmstom</td>
<td>Doxorubin/Cis</td>
<td>325</td>
<td>RT/cyst</td>
<td>T3,T4</td>
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<tr>
<td>Hall</td>
<td>CMV</td>
<td>975</td>
<td>RT/Cyst/Both</td>
<td>Yes</td>
</tr>
<tr>
<td>Grossman</td>
<td>MVAC</td>
<td>317</td>
<td>Cyst</td>
<td>Yes</td>
</tr>
</tbody>
</table>

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Neoadjuvant MRC/EORTC Trial

- Largest published trial to date
- 976* pts (CMV versus no chemotherapy)
- At 4 yrs, non-significant trend towards improved overall survival
- At 7.4 yrs, significant 6% absolute survival benefit
- Short course of chemotherapy (9 weeks) and inclusion of leucovorin rescue may have led to suboptimal eradication of micrometastases

*planned sample size sufficient to detect a 10% improvement in OS
Neoadjuvant Chemotherapy plus Cystectomy Compared with Cystectomy Alone for Locally Advanced Bladder Cancer

H. Barton Grossman, M.D., Ronald B. Natale, M.D., Catherine M. Tangen, Dr.P.H., V.O. Speights, D.O., Nicholas J. Vogelzang, M.D., Donald L. Trump, M.D., Ralph W. deVere White, M.D., Michael F. Sarosdy, M.D., David P. Wood, Jr., M.D., Derek Raghavan, M.D., Ph.D., and E. David Crawford, M.D.
### Table 4. Stratified and Unstratified Survival Analysis.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median Survival</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M-VAC and</td>
<td>Cystectomy</td>
</tr>
<tr>
<td></td>
<td>Cystectomy</td>
<td>Alone</td>
</tr>
<tr>
<td></td>
<td>months</td>
<td></td>
</tr>
<tr>
<td>Unstratified</td>
<td>77</td>
<td>46</td>
</tr>
<tr>
<td>Primary analysis, stratified according</td>
<td></td>
<td></td>
</tr>
<tr>
<td>to age and tumor stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>Stratified according to age</td>
<td></td>
<td>0.05</td>
</tr>
<tr>
<td>Age &lt;65 yr</td>
<td>104</td>
<td>67</td>
</tr>
<tr>
<td>Age ≥65 yr</td>
<td>61</td>
<td>30</td>
</tr>
<tr>
<td>Stratified according to tumor stage</td>
<td></td>
<td>0.05</td>
</tr>
<tr>
<td>T2</td>
<td>105</td>
<td>75</td>
</tr>
<tr>
<td>T3 or T4a</td>
<td>65</td>
<td>24</td>
</tr>
</tbody>
</table>

* There were 90 deaths in the combination-therapy group after a median follow-up of 8.7 years. There were 100 deaths in the cystectomy group after a median follow-up of 8.4 years. M-VAC denotes methotrexate, vinblastine, doxorubicin, and cisplatin.

† The log-rank test was used to calculate P values.
Survival among Patients Randomly Assigned to Receive Methotrexate, Vinblastine, Doxorubicin, and Cisplatin (M-VAC) Followed by Cystectomy or Cystectomy Alone, According to an Intention-to-Treat Analysis

Survival According to Treatment Group and Whether Patients Were Pathologically Free of Cancer (pT0) or Had Residual Disease (RD) at the Time of Cystectomy

Conclusions

- Median survival of cystectomy alone was 46 mo c/w 77 mo for combination therapy (p=0.06 by two-sided stratified log rank test)

- In both groups, improved survival associated with the absence of residual cancer in the cystectomy specimen

- Significantly more patients in the combination group had no residual disease than patients in the cystectomy group (38% vs. 15%, p=<0.001)
Conclusions

- The 38% rate of p0 achieved in this study and the significant survival of this subset of patients provides a strong rationale for considering a bladder-sparing approach in future studies.

» Can radical cystectomy be deferred?

» Can cystoscopy and urinary biochemical and molecular studies effectively identify and monitor patients achieving p0?
Review—Bladder Cancer

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

Meta-analysis Group, Medical Research Council Clinical Trials Unit, 222 Easton Road, London NW1 2DA, UK
Neoadjuvant chemotherapy confers a survival benefit and 85% achieving pT0 are alive at 5 years (Grossman, NEJM 2003).

Downstaging to ≤ pT1 or pT0 disease confers the greatest survival benefit (Splinter, JU 1992).

Gemcitabine and Cisplatin (GC) less toxic than MVAC with comparable survival (JCO 2005).

GC has evolved into the standard regimen for neoadjuvant chemotherapy in muscle-invasive urothelial carcinoma of the bladder but no data on efficacy.
Comparison of Outcomes

<table>
<thead>
<tr>
<th></th>
<th>GC (n=42)</th>
<th>MVAC (n=55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pT0</td>
<td>26% (95% CI 14, 42)</td>
<td>27% (95% CI 16, 41)</td>
</tr>
<tr>
<td>≤ pT1</td>
<td>36% (95% CI 21, 52)</td>
<td>36% (95% CI 24, 50)</td>
</tr>
<tr>
<td>LN positive</td>
<td>26% (95% CI 14, 42)</td>
<td>22% (95% CI 12, 35)</td>
</tr>
</tbody>
</table>

Median f/u survivors 30 months

Median f/u survivors 40 months

Median DFS 71 months (95% CI 52, 88)

National Cancer Institute
What does this mean for patients?

1. All patients should be informed about neoadjuvant chemotherapy benefits derived from data on over 3000 randomized patients on 12 randomized trials.
2. Patients tolerant of cisplatin-combination chemotherapy should get 3 months of neoadjuvant chemotherapy.
3. If the patient refuses, then adjuvant chemotherapy should be considered but the data are less compelling and derived from 150 patients on randomized 2 phase trials.

What does this mean for physicians practicing evidenced-based medicine?

1. Chemotherapy does not substitute for surgery; this is combined modality like testicular, ovarian and breast cancer.
2. A “little chemotherapy” or a “couple of cycles” doesn’t make sense in solid tumors.

Metastatic Bladder Cancer
Sites of Metastases

- Regional lymph nodes
- Bone
- Lung
- Liver
- Skin
- CNS (seen in chemotherapy treated pts)
Metastatic Bladder Cancer

- Many chemotherapy agents with activity in TCC e.g. CDDP, carboplatin, MTX, doxorubicin, vinblastine, ifosfamide, gemcitabine, paclitaxel and docetaxel
- MVAC found to improve OS c/w CDDP alone or CISCA
- A small proportion of patients (3-7%) can be cured with MVAC
- MVAC with significant toxicity
Chemotherapy for Metastatic Bladder Cancer: Median Survivals

Ifos, Taxol & Cisplatin (ITP)
Gemcitabine, paclitaxel & Cisplatin - GCT
Paclitaxel & Cisplatin
Gemcitabine & Cisplatin
Paclitaxel & Carboplatin
Paclitaxel
Gemcitabine
Randomized Phase III Study In Metastatic Bladder Cancer

**GC**
- Gemzar 1000 mg/m² day 1, 8 and 15
- Cisplatin 70 mg/m² day 2

**MVAC**
- Methotrexate 30 mg/m² day 1, 15 and 22
- Vinblastine 3 mg/m² day 2, 15 and 22
- Adriamycin 30 mg/m² day 2
- Cisplatin 70 mg/m² day 2

National Cancer Institute
## Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>G-C</th>
<th>MVAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized pts</td>
<td>203</td>
<td>202</td>
</tr>
<tr>
<td>Median age</td>
<td>63 years</td>
<td>63 years</td>
</tr>
<tr>
<td>PS $\geq$ 80</td>
<td>82.5%</td>
<td>81.1%</td>
</tr>
<tr>
<td>T $\text{any}$ N $\text{any}$ M1</td>
<td>69.5%</td>
<td>62.9%</td>
</tr>
<tr>
<td>Visceral Mets</td>
<td>48.8%</td>
<td>46.0%</td>
</tr>
<tr>
<td>High Alk Phos</td>
<td>28.6%</td>
<td>26.0%</td>
</tr>
<tr>
<td>$\geq$ 4 ds sites</td>
<td>20.7%</td>
<td>17.3%</td>
</tr>
</tbody>
</table>
## GC versus MVAC
### Most important toxicity differences

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>GC</th>
<th>MVAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenic fever</td>
<td>2%</td>
<td>14%</td>
</tr>
<tr>
<td>Neutropenic sepsis</td>
<td>1%</td>
<td>12%</td>
</tr>
<tr>
<td>Mucositis (grade 3/4)</td>
<td>1%</td>
<td>22%</td>
</tr>
<tr>
<td>Toxic deaths</td>
<td>1%</td>
<td>3%</td>
</tr>
</tbody>
</table>
## GC versus MVAC Survival Analysis

<table>
<thead>
<tr>
<th>Metric</th>
<th>G-C</th>
<th>MVAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Survival</td>
<td>13.8 months</td>
<td>14.8 months</td>
</tr>
<tr>
<td>Response Rate</td>
<td>49.4%</td>
<td>45.7%</td>
</tr>
<tr>
<td>CR</td>
<td>12.2%</td>
<td>11.9%</td>
</tr>
<tr>
<td>PR</td>
<td>37.2%</td>
<td>33.8%</td>
</tr>
<tr>
<td>SD</td>
<td>33.5%</td>
<td>32.5%</td>
</tr>
<tr>
<td>Median TTP</td>
<td>7.4 months</td>
<td>7.4 months</td>
</tr>
<tr>
<td>Median TTF</td>
<td>5.8 months</td>
<td>4.6 months</td>
</tr>
</tbody>
</table>
GC versus MVAC
Time to progressive disease

- **GC**: 7.4 months (6.6-8.1)
- **MVAC**: 7.4 months (6.7-9.1)
- **HR**: 1.05 (0.85-1.30)
GC versus MVAC
Overall survival

GC 13.8 months (12.3-15.8)
MVAC 14.8 months (13.2-16.8)
HR: 1.04 (0.82-1.32)
Urothelial Cancer
EORTC/Intergroup Study
[Bellmunt et al. Abstract # LBA5030, ASCO 2007]

- Phase III trial

**Metastatic urothelial cancer**
No prior systemic therapy

- Cisplatin 70mg/ m²
  + Gemcitabine 1000mg/ m²
  Days 1,8 and 15

- Cisplatin 70mg/ m²
  + Paciitaxel 80mg/ m²
  Days 1 and 8
  + Gemcitabine 1000mg/ m²
  Days 1 and 8
## Results
**(627 patients)**

<table>
<thead>
<tr>
<th></th>
<th>Cis+Gem</th>
<th>Cis+Tax+Gem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Med PFS</td>
<td>7.7 mos</td>
<td>8.8 mos</td>
</tr>
<tr>
<td>RR</td>
<td>46%</td>
<td>57% (p=0.02)</td>
</tr>
<tr>
<td>CR</td>
<td>10%</td>
<td>15%</td>
</tr>
<tr>
<td>Med surv</td>
<td>12.8 mos</td>
<td>15 mos</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(p=0.10)</td>
</tr>
<tr>
<td>Febrile Neutropenia</td>
<td>3.8%</td>
<td>12.5%</td>
</tr>
</tbody>
</table>

*National Cancer Institute*
Conclusion

- Triplet therapy improved response rates in metastatic bladder cancer
- Subset analysis revealed significant benefit for bladder primary and patients with 0 or 1 poor risk factors (PS of 1, or visceral mets)
- No statistically significant improvement in overall survival
- Hence current standard regimen remains cis+gem in metastatic disease
Therapies in metastatic disease after cisplatin based regimens

• Currently no established therapy in this setting

• As we use cisplatin and gem in neo/adjuvant setting, the evaluation of novel agents in frontline metastatic disease is even more important since we are likely treating disease refractory to this regimen.
Vinflunine + BSC vs BSC Alone in TCC of the Urothelium

Randomized 2:1

Patients with previously platinum-treated advanced TCC of the urothelium
(N = 370)

Vinflunine* + BSC
(n = 253)

BSC
(n = 117)

*Vinflunine dose based on ECOG PS and previous treatment
PS 0: 320 mg/m² every 3 weeks
PS 1 or PS 0 with previous pelvic irradiation: 280 mg/m² escalated to 320 mg/m²

Efficacy Results: Secondary Endpoints

<table>
<thead>
<tr>
<th>Number of Randomized Patients</th>
<th>Vinflunine + BSC (n = 253)</th>
<th>BSC (n = 117)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (IRC) evaluable patients</td>
<td>n = 185 16 (8.6) 5.0-13.7</td>
<td>P = .0063 n = 85 0</td>
</tr>
<tr>
<td>N (%) 95% CI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease control (%) IRC 95% CI</td>
<td>104 (41.1) 35.0-47.4</td>
<td>P = .0024 29 (24.8) 17.3-3.6</td>
</tr>
<tr>
<td>Disease control (%) IRC 95% CI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median duration of response, mos IRC 95% CI</td>
<td>7.4 4.5-17.0</td>
<td>-</td>
</tr>
<tr>
<td>Median duration of disease control, mos IRC 95% CI</td>
<td>5.7 5.0-6.3</td>
<td>- 4.2 3.8-4.9</td>
</tr>
<tr>
<td>Median PFS, mos IRC 95% CI</td>
<td>3.0 2.1-4.0</td>
<td>P = .0012 1.5 1.4-2.3</td>
</tr>
</tbody>
</table>

**OS Results: Eligible Patients**

<table>
<thead>
<tr>
<th></th>
<th>Vinflunine + BSC (n = 249)</th>
<th>BSC (n = 108)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of events</td>
<td>202</td>
<td>98</td>
</tr>
<tr>
<td>No. censored (%)</td>
<td>47 (18.9)</td>
<td>10 (9.3)</td>
</tr>
<tr>
<td>Median OS, mos (95% CI)</td>
<td>6.9 (5.7-8.0)</td>
<td>4.3 (3.8-5.4)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.78 (0.61-0.99)</td>
<td></td>
</tr>
<tr>
<td><em>P value</em></td>
<td>.0403</td>
<td></td>
</tr>
</tbody>
</table>

*Stratified log rank test.
**VEGF expression and signaling in UC**

- Microvessel density, a histological measure of angiogenesis, has been correlated with stage, recurrence and survival.
- Increased expression of VEGF occurs in the tissue, serum, and urine in UC patients and correlates with stage and prognosis.
- Inhibitors of angiogenesis are active in UC preclinical models.

Figure 3 An autocrine function of VEGF in T24 cells. Inhibition of T24 cell proliferation by blocking endogenous VEGF expression. Cells were treated with anti-VEGF antisense oligonucleotide for 3 days. $[^3]H$thymidine (1 μCi/ml) was added to the culture during the last 4 h of incubation and cell proliferation determined by measuring the incorporation of $[^3]H$thymidine into DNA. The experiment was conducted with triplicate samples and repeated at least twice with similar results. In all, 5 and 10 μM of anti-VEGF antisense oligonucleotide significantly reduces the $[^3]H$thymidine incorporation in T24 cells compared with scrambled control oligonucleotide ($P<0.0005$ and $P<0.00004$, respectively).
ASCO 2010: Phase 2 first-line study of GC + bevacizumab (Hahn et al) – Abstract 4051

Key Eligibility Criteria
- Metastatic UC (mUC)
- ECOG PS 0-1
- Cr < 1.5 mg/dl
- No prior CTx for mUC
- No anticoagulation
- No CNS mets

Cisplatin
70 mg/m² iv d1

Gemcitabine*
1000-1250 mg/m² iv d1,8

Bevacizumab
15 mg/kg iv d1

Cycle length = 21 days
Update on phase 2 first-line study of GC + bevacizumab (Hahn et al)

ORR = 72%

<table>
<thead>
<tr>
<th>Response Type</th>
<th>N</th>
<th>% (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response*</td>
<td>8</td>
<td>19 (8-33)</td>
</tr>
<tr>
<td>Partial Response</td>
<td>23</td>
<td>53 (31-62)</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>7</td>
<td>16 (7-31)</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>5</td>
<td>12 (4-25)</td>
</tr>
</tbody>
</table>

*Note: 3 patients underwent cystectomy for clinical CR. Pathologic results included – pTis N0, pT1 N2, pT3 N0
Update on phase 2 first-line study of GC + bevacizumab (Hahn et al)

The primary study PFS endpoint was not achieved
Update on phase 2 first-line study of GC + bevacizumab (Hahn et al)

Median OS = 19.1 months
95% CI (12.4 – 22.5)
Median Follow-up = 27.2 months
Range (1.6-40.9)
CALGB 90601TCC Trial: GC +/- Bevacizumab

- Metastatic TCC and/or
- Unresectable TCC
- Minimum CrCl 60 cc/m
- No Prior Chemotherapy

Toxicity monitoring with 5 planned analyses

PI - J. Rosenberg, MD
Sunitinib in Second-line for Metastatic UC

ASCO 2010: First-line sunitinib in cisplatin ineligible pts (Bellmunt et al) – Abstract 4540

- First-line sunitinib monotherapy (n=38)
  - 50 mg/day (Schedule 4/2)
- Median age = 75
- Majority with bladder primary
- Visceral metastases (47%)
  - lung (29%), liver (10%), bone (8%)
- CDDP “unfit” criteria
  - CrCl < 60 ml/min but > 30 ml/min
- ECOG PS ≤ 1
Renal impairment and cisplatin eligibility

Using the CG equation, >40% of patients age >70 years are ineligible.

## Selected Non-Cisplatin Regimens

<table>
<thead>
<tr>
<th>Study</th>
<th>Trial</th>
<th>Regimen</th>
<th>ORR (%)</th>
<th>Median Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bellmunt et al. 1997</td>
<td>Phase 2</td>
<td>M-CAVI</td>
<td>39%</td>
<td>9</td>
</tr>
<tr>
<td>Dogliotti et al. 2007</td>
<td>Phase 2</td>
<td>Gem/Carbo</td>
<td>40%</td>
<td>9.8</td>
</tr>
<tr>
<td>Meluch et al.* 2001</td>
<td>Phase 2</td>
<td>Pac/Gem</td>
<td>54%</td>
<td>14.4</td>
</tr>
<tr>
<td>Gitlitz et al. 2003</td>
<td>Phase 2</td>
<td>Gem/Doc</td>
<td>33%</td>
<td>13</td>
</tr>
<tr>
<td>Neri et al. 2002</td>
<td>Phase 2</td>
<td>Gem/Epi</td>
<td>57%</td>
<td>16</td>
</tr>
<tr>
<td>Bellmunt et al. 2010</td>
<td>Phase 2</td>
<td>Sunitinib</td>
<td>9%</td>
<td>8.1</td>
</tr>
<tr>
<td>Quinn et al. 2010</td>
<td>Phase 2</td>
<td>Eribulin</td>
<td>38%</td>
<td>9.4</td>
</tr>
</tbody>
</table>

* Includes previously treated patients
Summary

- Bladder cancer is one of the most common and deadly cancers
- Neoadjuvant chemotherapy improves survival in patients with muscle invasive disease
- Role and regimens of adjuvant chemo still require more studies.
- GC is an alternative and less toxic therapy than MVAC for metastatic BC.
- Newer combinations and additional targeted therapy trials are needed