Management of Ca Urinary Bladder

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Learning Objectives

Workup
Classification of Bladder Cancer: Non-Invasive & Invasive
Risk Stratification: High Low & Intermediate
Management of Invasive & Noninvasive Bladder Cancers
Local & Systemic Therapies, their integration
Management of Metastatic Disease
Treatment related complications
Recurrences & Management
Workup

- Full blood count and biochemical profile
- Urine cytology
- Cystoscopy
- Imaging of the urothelium (e.g., ultrasound, intravenous urogram, or computed tomography [CT] urogram)
- Muscle-invasive bladder cancer (MIBC) : detailed cross-sectional staging with CT or magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis.
- If any features suggestive of bone metastasis (e.g., raised alkaline phosphatase, bone pain): an isotope bone scan is indicated.
- Examination under anesthetic coupled with TURBT
Workup

- Presence or absence of a mass after TURBT: Important prognostic factor as it potentially indicates either unsuccessful clearance of tumor, extra-vesical extension, or both.
- TURBT serves as both definitive staging of the bladder lesion as well as a substantial proportion of the initial treatment.
- Pathological review of the resected specimen: to ascertain whether muscle invasion is present or not, particularly if the tumor appears sessile or high grade and whether there is CIS;
- These are the key determinants of further investigation and treatment
NON-INVASIVE CA

INVASIVE CA

Stage 0
Stage 1
Stage II
Stage III
Stage IV

Bladder

Muscle
Peritoneum
Fat
Non-muscle-Invasive & Invasive Bladder Cancer

- Stage Ta, T1, and carcinoma in situ [Tis]
- High recurrence rate - 50% - 70% after treatment by TURBT
- 10% to 20% of NMIBC : progresses to muscle invasion (≥T2 lesions)
- Tumor grade & stage, tumor number, size, presence of carcinoma in situ (CIS), recurrence rate, and age at diagnosis are risk factors of progression
- Invasive Disease: poor prognosis due to a very high rate of occult metastatic disease at the time of diagnosis(<10% present with metastatic disease)
- carries a poor prognosis
Non-muscle-Invasive Bladder Cancer

Base of the resected area should be separately biopsied. Any suspicious areas in the remainder of the bladder should be biopsied, Many advocate additional selected biopsies of the bladder mucosa and a prostatic urethral biopsy as well. (Urethral biopsies are clearly indicated in patients with risk factors for urethral involvement.) T1, G3 tumors, without muscularis propria in the specimen require second biopsy in order to obtain muscularis propria to reduce the risk of understaging.

Following resection of the tumor, a single dose of intravesical mitomycin-C for 1 hour within 24 hours of surgery reduces relative risk of recurrence by 24.2% but no impact on disease progression or survival.
Non-muscle-Invasive Bladder Cancer: Low V/S High Risk

- Low-risk tumors: single tumors <3 cm in diameter, graded as G1, staged as Ta, with no evidence of CIS.
- Intermediate- and high-risk tumors are defined using a scoring system based on a number of clinical and pathological factors:
  - Number of tumors
  - Tumor size
  - Prior recurrence rate
  - T category
  - Presence of concurrent CIS
  - Tumor grade
- Intermediate-risk tumors: up to a 38% probability of recurrence and a 5% risk of progression at 1 year.
- High-risk tumors: 61% probability of recurrence and a 17% risk of progression at 1 year.
EORTC Risk Tables for Predicting Recurrence and Progression in Individual Patients with Stage Ta T1 Bladder Cancer

The provided software implements the EORTC Scoring System and Risk Tables for Stage Ta T1 Bladder Cancer as published in the paper:


They allow the user to estimate the probability of recurrence and progression in patients with stage Ta T1 bladder cancer based on six different factors:

- Number of tumors
- Tumor size
- Prior recurrence rate
- T category
- Concomitant carcinoma in situ
- Grade

Download the calculator

(Versions are available for Windows, iPhone/iPad and Android phones/tablets)

Windows software programmed by Richard Sylvester, EORTC Headquarters.

iPhone/iPad and Android versions have been developed in cooperation with Cambridge Laboratories, a division of Alliance Pharmaceuticals Ltd.
Management: Non-muscle-Invasive Bladder Cancer

Management strategy are based on accurate initial staging and grading of the disease. There can be variation in the interpretation of pathological specimens, so review of pathology is recommended. If there is uncertainty over the pathology, a further early re-resection is indicated.

Low-risk tumors: 15% probability of recurrence and a 0.2% risk of progression at 1 year. Cystoscopy 3 months after the initial resection, and if this is negative, a flexible cystoscopy should be undertaken 9 months later and then annually thereafter.
Management: Non-muscle-Invasive Bladder Cancer

• Patients who are at significant risk for developing progressive or recurrent disease following TURBT: candidates for adjuvant intravesical drug therapy.

• This includes those with multifocal CIS, CIS associated with Ta or T1 tumors, any G3 tumor, multifocal tumors, and those whose tumors rapidly recur following TURBT of the initial bladder tumor.

• Number of drugs have been used intravesically: Bacillus Calmette-Guérin (BCG), interferon (IFN) and BCG, thioTEPA, mitomycin C, doxorubicin, and gemcitabine.
Management: Non-muscle-Invasive Bladder Cancer

A number of studies have compared one intravesical chemotherapeutic agent with another. For the most part, BCG in these comparisons has a slight advantage in reducing recurrences.

However, at FU more than 5 years, it appears that there is minimal overall effect at reducing the recurrence rate when compared with no treatment.

BCG and Epirubicin are the most commonly used agents.

Both are effective for the treatment of superficial bladder cancer. However, superiority of one over the other is unknown.

A meta-analysis of over 1,100 patients treated with either drug reported that intravesical BCG was more efficacious, although also more toxic.
Management: NMIBC, Intravesical Treatment

Variety of treatment schedules in the literature
Commonly used schedule: intravesical treatment once a week for 6 weeks followed by a subsequent 3 weeks as an induction treatment.

If there is no cystoscopic evidence of recurrence, the patient to be offered ongoing maintenance BCG with 3-6 week courses of BCG every 3 to 6 months with regular cystoscopic surveillance.

In a recent meta-analysis of trials with BCG maintenance, a 32% reduction in the risk of recurrence was seen for BCG compared with mitomycin-C (P < .0001), whereas there was a 28% increase in the risk of recurrence (P = .006) for patients treated with BCG in the trials without BCG maintenance.
Management: NMIBC, Intravesical Treatment

Choice of treatment depends on risk of recurrence and progression based on EORTC subgroups.

Low risk recurrence subgroup: BCG does not alter the natural course of tumors therefore its use considered to be overtreatment.

Patients with high risk of progression: BCG treatment including at least 1-year maintenance, is indicated.

In this subgroup BCG with 1-year maintenance is more effective than chemotherapy for prevention of recurrence; however, also more side effects than chemotherapy.

The final choice should reflect the individual patient’s risk of recurrence and progression and the efficacy and side effects of each treatment modality (EAU guidelines).

In treatment refractory disease, the patient should be offered radical treatment for the bladder.
Muscle-Invasive, Non-metastatic Disease

20% to 40% will either present with or ultimately develop muscle-invasive disease.

Muscle-invasive bladder cancer: lethal malignancy, if untreated over 85% of patients will die of the disease within 2 years of diagnosis.

Aggressive treatment approach employing radical cystectomy for high-grade, invasive bladder cancer

– Good long-term survival rates, lowest local recurrences
– Morbidity and mortality substantially improved over the past several decades.
– It provides accurate pathologic staging of the primary bladder tumor (p stage) and regional lymph nodes, thus, selectively determining the need for adjuvant therapy based on precise pathologic evaluation.
Muscle-Invasive, Non-metastatic Disease: Surgical Management

Males: Cystoprostatectomy, with or without a urethrectomy and bilateral pelvic lymph node dissection

Female: an anterior exenteration, which includes the bladder and urethra (the urethra may be spared if uninvolved and an orthotopic bladder reconstruction is performed), the ventral vaginal wall, and the uterus.

A radical cystectomy may be indicated in non–muscularis propria–invasive bladder cancers when G3 disease is multifocal or associated with CIS or when bladder tumors rapidly recur, particularly in multifocal areas following intravesical drug therapy.
An appropriate lymphadenectomy is an important component of radical cystectomy. Related to the clinical outcomes of patients with high-grade, invasive bladder cancer, evidence suggests that a more extended lymphadenectomy is beneficial in both lymph node–positive and lymph node–negative patients with bladder cancer. Removal of more than 15 lymph nodes has been postulated to be both sufficient for the evaluation of the lymph node status as well as beneficial for overall survival in retrospective studies. Both laparoscopic and robot-assisted cystectomy have been shown to be feasible and safe, but with a relatively shorter follow-up.
Muscle-Invasive, Non-metastatic Disease: Surgical Management

Partial cystectomies may rarely be performed in selected patients, thus preserving bladder function in properly selected patients, same cure rate as a radical cystectomy.

Candidates for such procedures must have focal disease located far enough away from the ureteral orifices and bladder neck, to achieve at least a 2-cm margin around the tumor and a margin sufficient around the ureteral orifices and bladder neck to reconstruct the bladder.

Practically, this limits partial cystectomies to those patients who have small tumors located in the dome of the bladder and in whom random bladder biopsies show no evidence of CIS or other bladder tumors.
Types of Urinary Diversion

• Divided into continent and incontinent.
• Incontinent urinary diversions or conduits involve the use of a segment of ileum or colon and, less commonly, a segment of jejunum.
• The distal end is brought to the skin, and the ureters are implanted into the proximal end.
• The patient wears a urinary collection appliance.
• The advantages of a conduit (ileal or colonic) are its simplicity and the reduced number of immediate and long-term postoperative complications.
Types of Urinary Diversion

- Continent diversions may be divided into two types: abdominal and orthotopic.
- Abdominal diversions require a continence valve, whereas an orthotopic neobladder depends on the urethral sphincter for continence.
- The reservoir is made of bowel that is fashioned into a globular configuration.
- Abdominal type of continent diversion: stoma is brought through the abdominal wall to the skin. The patient catheterizes the pouch every 4 hours.
- Orthotopic urinary diversions that use of bowel brought to the urethra, thus allowing the patient to void by Valsalva.
- Advantage of continent diversions:
  - avoidance of a collection device,
  - rehabilitates the patient to normal voiding through the urethra, often without the need for intermittent catheterization or the need to wear a collection device.
## Survival at 10 Years After Radical Cystectomy

<table>
<thead>
<tr>
<th>Pathologic Stage</th>
<th>Disease-Specific Survival (%)</th>
<th>Overall Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pTa, Tis, T1 with high risk of progression</td>
<td>82</td>
<td>—</td>
</tr>
<tr>
<td>Organ confined, negative nodes (pT2, pN0)</td>
<td>73</td>
<td>49</td>
</tr>
<tr>
<td>Non–organ confined (pT3–4a or pN1–2)</td>
<td>33</td>
<td>23</td>
</tr>
<tr>
<td>Lymph node positive (any T, pN1–2)</td>
<td>28, 34</td>
<td>21</td>
</tr>
</tbody>
</table>
Selective Bladder-Preserving Approaches

For selected patients, bladder sparing therapy with salvage cystectomy reserved for tumor recurrence: safe and effective alternative to immediate radical cystectomy.

TURBT of as much of the tumor as is safely possible, followed by the combination of radiation with concurrent radiosensitizing chemotherapy.

Selection of patients for bladder preservation on the basis of the initial response of each individual patient’s tumor to therapy: Important for success.

Bladder conservation is reserved for patients who have a clinical CR to concurrent chemotherapy and radiation.

Prompt cystectomy is recommended if tumors respond incompletely or who subsequently develop an invasive tumor.

Up to 30% of the patients entering a potential bladder-preserving protocol with trimodality therapy.
Management: Bladder Preservation

- Tumor presentations associated with successful bladder-sparing therapy include:
  - solitary T2 or early T3 tumors (typically <6 cm in size),
  - no tumor-associated hydronephrosis, tumors allowing a visibly complete TURBT,
  - invasive tumors not associated with extensive CIS,
  - urothelial carcinoma histology

- Age is not a contraindication to successful bladder sparing therapy, and indeed, results are favorable in patients aged 75 years or

- Bladder-sparing chemoradiation remains a good option for those patients who are not cystectomy candidates and

- Such patients can be treated with daily radiation and appropriate concurrent chemotherapy without a break.
Bladder-Preserving Approach

TURBT

XRT (40 Gy) + Concomitant chemotherapy

Cystoscopic response evaluation

Complete response

Consolidation Chemoradiation (64Gy)

Incomplete response

Radical cystectomy

Recurrent tumor
**Bladder-Preserving Approach: Results**

<table>
<thead>
<tr>
<th>Series, year</th>
<th>Multimodality Therapy Used</th>
<th>Number of Patients</th>
<th>5-Year Overall Survival (%)</th>
<th>5-Year Survival with Intact Bladder (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTOG 8512, 1993</td>
<td>External-beam radiation with cisplatin</td>
<td>42</td>
<td>52</td>
<td>42</td>
</tr>
<tr>
<td>RTOG 8802, 1996</td>
<td>TURBT, MCV, external-beam radiation with cisplatin</td>
<td>91</td>
<td>51</td>
<td>44 (4 y)</td>
</tr>
<tr>
<td>RTOG 8903, 1998</td>
<td>TURBT with or without MCV, external-beam radiation with cisplatin</td>
<td>123</td>
<td>49</td>
<td>38</td>
</tr>
<tr>
<td>University of Paris, 1998</td>
<td>TURBT, 5-FU, external-beam radiation with cisplatin</td>
<td>120</td>
<td>63</td>
<td>N/A</td>
</tr>
<tr>
<td>Erlangen, 2002</td>
<td>TURBT, external-beam radiation, cisplatin, carboplatin, or cisplatin and 5-FU</td>
<td>415 (cisplatin, 82; carboplatin, 61; 5-FU/cisplatin, 87)</td>
<td>51</td>
<td>42</td>
</tr>
<tr>
<td>RTOG 9906, 2009</td>
<td>TURBT, TAX plus CP plus XRT; adjuvant CP plus GEM</td>
<td>80</td>
<td>56</td>
<td>47</td>
</tr>
<tr>
<td>MGH, 2012</td>
<td>TURBT, external-beam radiation and cisplatin with or without 5-FU or TAX; neoadjuvant or adjuvant chemotherapy</td>
<td>348</td>
<td>52</td>
<td>42</td>
</tr>
</tbody>
</table>
# Results: Surgery v/s Bladder Preservation

<table>
<thead>
<tr>
<th>Series, Yr.</th>
<th>Stages</th>
<th>Number of Patients</th>
<th>Overall Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>5 Year</td>
</tr>
<tr>
<td><strong>Cystectomy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>University of Southern California, 2001</td>
<td>pT2–pT4a</td>
<td>633</td>
<td>48</td>
</tr>
<tr>
<td>Memorial Sloan-Kettering, 2001</td>
<td>pT2–pT4a</td>
<td>181</td>
<td>36</td>
</tr>
<tr>
<td>SWOG/ECOG/CALGB, 2003</td>
<td>cT2–cT4a</td>
<td>303</td>
<td>49</td>
</tr>
<tr>
<td><strong>Selective Bladder Preservation (Chemoradiation)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>University of Erlangen, 2002</td>
<td>cT2–cT4a</td>
<td>326</td>
<td>45</td>
</tr>
<tr>
<td>MGH, 2012</td>
<td>cT2–cT4a</td>
<td>348</td>
<td>52</td>
</tr>
<tr>
<td>RTOG, 1998</td>
<td>cT2–cT4a</td>
<td>123</td>
<td>49</td>
</tr>
<tr>
<td>BC2001, 2012</td>
<td>cT2–4a</td>
<td>182</td>
<td>48</td>
</tr>
</tbody>
</table>
Radiation Treatment

Treatment of the pelvis to include the

- Bladder, prostate (in men),
- Low external and internal iliac lymph nodes
- total dose of 40 to 45 Gy / 1.8-2.0-Gy#/ 4 - 5 weeks.
- Subsequently, the target volume is reduced to deliver a final boost dose of 20 -25 Gy / 15 # to the primary bladder tumor.

Higher doses per fraction may lead to a higher rate of significant late complications.

Bladder be emptied when simulated and prior to each treatment to maximize reproducibility and avoid a geographic miss.

Forms of image-guided delivery (including daily cone-beam CT and fiducials) have also been employed for accurate localization

Brachytherapy is another technique to deliver a higher dose of radiation to a limited area of the bladder within a short period.
## Radiation Treatment

### TABLE 64.7 INDICATIONS FOR RADIOThERAPY IN BLADDER CANCER

<table>
<thead>
<tr>
<th>Stage</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIS, Ta, T1</td>
<td>No role for radiotherapy</td>
</tr>
<tr>
<td>T2-T4aN0M0</td>
<td>Potential role for radiotherapy, combined with synchronous chemotherapy if patient sufficiently fit</td>
</tr>
<tr>
<td>TanyN1–3M0 or TanyNanyM1</td>
<td>No role for radical radiotherapy as sole treatment for stage IV disease. It may be worth considering, however, as part of a package of “radical” palliation in concert with systemic chemotherapy. No randomized data on the use of radiotherapy in this setting beyond studies of fractionation.</td>
</tr>
</tbody>
</table>
Preoperative Irradiation

Investigated in the past, but interest in the technique has waned due to the chemosensitivity of bladder cancer, which led to a lot of NACT trials in the 1980s & 1990s, ending the interest. Most studies in the literature are old, retrospective, nonrandomized comparisons, and little can be concluded from them, with few randomized trials in the literature.

Parsons and Million reviewed the results of retrospective studies and six prospective randomized trials on the use of preoperative irradiation, concluding that the use of the technique may improve outcomes by up to 15% to 20% at 5 years. They also observed that many preoperative RT series report pathological CR rates of around one-third, similar to that seen with NACT.

No modern trials of preoperative radiotherapy.
Postoperative Radiotherapy

- Little in the way of randomized data on the use of adjuvant radiotherapy following surgery.
- When used, it is mostly based on the grounds of positive surgical margins or tumor spillage at surgery,
- Chemo-naive patients at high risk of recurrence can be offered adjuvant chemotherapy in Post-op setting, although the evidence base for this approach is also somewhat thin.
- What few data there are on radiotherapy suggests that limited doses are well tolerated.
Systemic Chemo for Radical Therapy: NACT

NACT advantages
- potential to downsize and downstage tumors
- attack occult metastatic disease early, as postoperative complications and prolonged recovery can delay adjuvant chemotherapy.

NACT Disadvantages
- inherent difficulties in assessing response, the fact that clinical rather than pathologic criteria must be relied on,
- the debilitating effects of chemotherapy in some patients, increasing the risks of surgery and possibly complicating or delaying full recovery from surgery,
- possibility of the deleterious effects of the delay in cystectomy or radiation associated with NACT, may lead to disease progression in a proportion of nonresponding patients

2 Phase III trials suggest a survival advantage for NACT
4 meta-analyses have been published that showed a 4% to 6% absolute increase in 5-year survival with NACT
GC, standard or accelerated or MVAC are widely used with definitive radical treatment
In the future, gene profiling may identify those most likely to respond to chemotherapy.
Systemic Chemo for Radical Therapy: Adjuvant CT

Advantage: pathologic staging allows for a more accurate selection of patients. – facilitates the separation of patients in stage pT2 from patients at a high risk for metastatic progression (stages pT3/pT4 or node+ive disease).

Adjuvant CT studied in two major clinical settings:
– Following bladder-sparing chemoradiation: no guidance from pathologic staging, but studies show that up to 50% of those with invasive cancers can have systemic disease.
– Following a radical cystectomy.

Adjuvant chemotherapy after cystectomy: studied more thoroughly, but again, the results are not clear.

Adjuvant chemotherapy may improve survivals in positive nodes (even with negative nodes) and high pathologic stage of the primary tumor.

Advanced Bladder Cancer Meta-Analysis Collaboration: 491 patients from six trials, insufficient evidence, recommended further research

More recent studies have used different adjuvant chemotherapy regimens or molecular stratification.
Treatment of Local–Regionally Advanced Disease

Carefully selected patients with locally advanced unresectable bladder cancer, including some with pelvic nodal masses, may experience long-term survival with the combination of chemotherapy and radiation.

Initial treatment of four to six cycles of combination CT.

If a significant regression achieved, radiation is administered in combination with radiosensitizing chemotherapy in carefully selected patients.

To be selected for this combined modality treatment, patients must have:

- an excellent performance status,
- locally advanced measurable disease,
- normal kidney function tests, and
- no evidence of distant metastases beyond the common iliac lymph nodes.
Multimodality Management

Biopsy-proven muscle-invasive bladder cancer

Maximal transurethral resection of tumor

Induction chemoradiotherapy 3 weeks

Cystoscopy and biopsy week 7

T0 or noninvasive disease only

Consolidation chemoradiotherapy weeks 8–9

Cystoscopy and biopsy week 17

T0

Ta or Tis disease

T1+ disease

Surveillance

Intravesical therapy

Salvage cystectomy

Residual disease or new T1+

Cystectomy

Adjuvant chemotherapy in selected cases
Multimodality Management

- Neoadjuvant chemotherapy
  - Cystectomy
  - Radiotherapy
    - Salvage cystectomy
    - Radiotherapy on relapse
    - Cystectomy
      - Adjuvant chemotherapy in selected cases
Metastatic Bladder Cancer

Bladder cancer metastasizes most commonly to the lungs, bone, liver, and brain. Prognosis is poor, with a median survival on the order of only 12 months. Cisplatin-Based Combination Chemo, the standard chemotherapy regimen for advanced bladder cancer for more than a decade, was MVAC.

Another commonly used regimen is CMV, (omits the doxorubicin, somewhat less toxicity)

Gem-Cis was compared with MVAC in a multicenter phase III study. Median survival was 14 months with GC & 15.2 months with MVAC, which were statistically comparable.

Patients treated with GC, however, had significantly less toxicity and improved tolerability.

As a result of this study, GC is generally considered the current standard of care for metastatic bladder cancer.
### Metastatic Bladder Cancer: Chemo Results

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Agents (Ref.)</th>
<th>Schedule</th>
<th>Composite Number of Assessable Patients</th>
<th>Complete Response (%)</th>
<th>Response Rate (%)</th>
<th>Median Survival (Mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MVAC</td>
<td>Methotrexate</td>
<td>30 mg/m² d 1, 15, 22</td>
<td>374</td>
<td>12–35</td>
<td>39–65</td>
<td>12.5–14.8</td>
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<tr>
<td></td>
<td>Vinblastine</td>
<td>3 mg/m² d 2, 15, 22</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Doxorubicin</td>
<td>30 mg/m² d 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cisplatin</td>
<td>70 mg/m² d 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMV</td>
<td>Cisplatin</td>
<td>70 mg/m² d 2</td>
<td>104</td>
<td>10</td>
<td>36</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Methotrexate</td>
<td>30 mg/m² d 1, 8</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Vinblastine</td>
<td>4 mg/m² d 1, 8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GC</td>
<td>Gemcitabine</td>
<td>1000 mg/m² d 1, 8, 15</td>
<td>203</td>
<td>12</td>
<td>49</td>
<td>13.8</td>
</tr>
<tr>
<td></td>
<td>Cisplatin</td>
<td>70 mg/m² d 2</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Taxane and Platinum-Containing Regimens

The doublets of cisplatin and paclitaxel and cisplatin and docetaxel appear to have response rates comparable to that of GC. Trials with carboplatin suggest that this agent has good activity, although likely not the same level of activity as cisplatin.

Triplet Chemotherapy

In phase II trials, three such combinations, including cisplatin/gemcitabine/paclitaxel, carboplatin/gemcitabine/paclitaxel, & cisplatin/gemcitabine/docetaxel, demonstrated high CR rates of 28% to 32%, and overall RRs of 66% to 78%,
## Metastatic Bladder Cancer: Chemo Results

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Composite Number of Patients</th>
<th>Response Rate (%)</th>
<th>Median Survival (Mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin/paclitaxel</td>
<td>104</td>
<td>21–65</td>
<td>8.5–9.5</td>
</tr>
<tr>
<td>Cisplatin/paclitaxel</td>
<td>52</td>
<td>50</td>
<td>10.6</td>
</tr>
<tr>
<td>Cisplatin/docetaxel</td>
<td>129</td>
<td>52–60</td>
<td>8.0–13.6</td>
</tr>
<tr>
<td>Cisplatin/gemcitabine/paclitaxel</td>
<td>61</td>
<td>78</td>
<td>15.8</td>
</tr>
<tr>
<td>Carboplatin/gemcitabine/paclitaxel</td>
<td>49</td>
<td>68</td>
<td>14.7</td>
</tr>
<tr>
<td>Cisplatin/gemcitabine/docetaxel</td>
<td>35</td>
<td>66</td>
<td>15.5</td>
</tr>
<tr>
<td>Gemcitabine/paclitaxel</td>
<td>94</td>
<td>54–60</td>
<td>14.4</td>
</tr>
</tbody>
</table>
A triplet of paclitaxel, cisplatin, and infusional high-dose 5-FU with leucovorin has also been studied.
Response rates: 75%, 28% CRs, median OS of 17 months.
Significant toxicity: myelosuppression, GI disturbances, infections, and two treatment-related deaths
A randomized phase III trial compared the standard GC regimen with GC plus paclitaxel (PCG).
Preliminary results and updated data showed despite a response rate that was superior in the three drug arm (55.5% versus 43.6%, p = 0.0031) and a median OS that was slightly longer in patients receiving the third drug (15.8 months versus 12.7 months), the HR for survival did not achieve statistical significance (HR, 0.85; p = 0.075).
Thus, the standard of care remains the doublet of gemcitabine plus cisplatin.
Immunotherapy in metastatic bladder cancer

FDA Approves New Immunotherapy Drug for Bladder Cancer

Subscribe
June 7, 2016, by NCI Staff

The Food and Drug Administration (FDA) on May 18 approved atezolizumab (Tecentriq®) for the treatment of some patients with urothelial carcinoma, the most common type of bladder cancer. The drug, which strengthens the body’s immune response against cancer, is the first new treatment approved for bladder cancer in two decades.

“This is very exciting news for patients with bladder cancer,” said Piyush Agarwal, M.D., head of the Bladder Cancer Section in the NCI Center for Cancer Research’s (CCR) Urologic Oncology Branch, who noted that the approval would likely

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Complications of Cystectomy and Urinary Diversion

Diversion-related complication: Metabolic, neuromechanical, and surgical

Electrolyte abnormalities and altered drug metabolism, metabolic acidosis

Neuromechanical: an atonic segment with urinary retention, and hyperperistaltic contractions.

Most common early diversion-unrelated complication is dehydration

Specific Surgical compilations of radical cystectomy can be short term or late.

Short-term complications
- acute acidosis (16%),
- urine leak (3% to 16%),
- bowel obstruction or fecal leak (10%), and
- pyelonephritis (5% to 15%).

Long term complications
- ureteral or intestinal obstruction (15%),
- renal deterioration (15%),
- renal failure (5%), stoma problems (15%), and
- intestinal stricture (10% to 15%).
Complications of Local Treatment

Complications generally include frequency, dysuria, and irritative voiding symptoms.

Over the long term, bladder contracture may occur with these agents. Other complications, which are specific for each drug, are as follows:

- BCG administration may result in fever, joint pain, granulomatous prostatitis, sinus formation, disseminated tuberculosis, and death.
- ThioTEPA may cause myelosuppression.
- Mitomycin C may cause skin desquamation and rash.
- Doxorubicin may cause gastrointestinal upset and allergic reactions.
Recurrences: Following Radical Cystectomy

- Classified as local (pelvic), distant, and urethral
- Local recurrences were defined as those occurring within the soft tissue field of exenteration. Incidence- 6% to 9%
- Distant recurrences were defined as those occurring outside the pelvis, 20% to 35% are reported in large series
- While urethral tumors were classified as a new primary tumor occurring in the retained urethra. Incidence 6% to 10%
Recurrences: Chemo-radiotherapy

Any recurrence: 93/182 pts

Loco-regional recurrence: 53
- Non-muscle invasive: 25
- Muscle invasive: 18
- Pelvic nodes: 6

Distant recurrence or second primary: 40
- Metastasis: 29
- Second primary: 11
Recurrences: Chemo-radiotherapy

- Majority of locoregional failures are in the bladder, and there are more noninvasive than invasive recurrences.
- This underlines the need for regular surveillance post radiotherapy and the requirement for good integration of radiotherapy and surgical services if patients are to be managed by bladder conservation.
- Majority of noninvasive recurrences can be successfully managed conservatively without the need for cystectomy.
- For those with invasive recurrence, cystectomy remains an option if the patients are sufficiently fit.
Treatment of Patients with Uncommon Bladder Tumors

- Squamous cell carcinoma: local failure may be more prevalent than distant relapse
- Surgical resection with a partial cystectomy and en bloc resection of the urachal ligament with umbilicus is the treatment of choice in the setting of localized disease.
- There is currently no definitive role for neoadjuvant or adjuvant chemotherapy in this tumor
- No standard chemotherapy regimen for these patients
- Small cell carcinoma: generally get treated along the same lines as small cell lung carcinoma
Thanks