Systemic Therapy Update in the Management of Bladder Cancer

By

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Systemic Therapy Update in the Management of Bladder Cancer

- Introduction
- Neoadjuvant systemic therapy
- Adjuvant systemic therapy
- Multimodality therapy and organ preservation
- Treatment of advanced/metastatic disease
Estimated age-standardized incidence rates (World) in 2018, worldwide, males, all ages

- Lung
- Prostate
- Colorectum
- Stomach
- Liver
- Bladder
- Oesophagus
- Non-Hodgkin lymphoma
- Leukaemia
- Kidney

Data source: GLOBOCAN 2018
Graph production: Global Cancer Observatory (http://gco.iarc.fr)

ASR (World) per 100,000
Public-domain database

- Coverage 21% of Egypt population
- Covering upper, middle and lower Egypt
Estimated number of new cases in 2018, Egypt, both sexes, all ages

<table>
<thead>
<tr>
<th>ICD</th>
<th>Top 10 cancers</th>
<th>Number</th>
<th>Crude Rate*</th>
<th>ASR (World)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>C00-97</td>
<td>All cancers</td>
<td>128,892</td>
<td>129.7</td>
<td>156.9</td>
</tr>
<tr>
<td>C22</td>
<td>Liver</td>
<td>25,399</td>
<td>25.6</td>
<td>32.2</td>
</tr>
<tr>
<td>C50</td>
<td>Breast</td>
<td>23,081</td>
<td>47.0</td>
<td>52.4</td>
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<tr>
<td>C82-86, C96</td>
<td>Non-Hodgkin lymphoma</td>
<td>9,854</td>
<td>9.9</td>
<td>11.8</td>
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<tr>
<td>C67</td>
<td>Bladder</td>
<td>9,239</td>
<td>9.3</td>
<td>11.9</td>
</tr>
<tr>
<td>C33-34</td>
<td>Lung</td>
<td>6,045</td>
<td>6.1</td>
<td>7.6</td>
</tr>
<tr>
<td>C18-21</td>
<td>Colorectum</td>
<td>5,393</td>
<td>5.4</td>
<td>6.5</td>
</tr>
<tr>
<td>C70-72</td>
<td>Brain, nervous system</td>
<td>4,555</td>
<td>4.6</td>
<td>5.2</td>
</tr>
<tr>
<td>C91-95</td>
<td>Leukaemia</td>
<td>4,314</td>
<td>4.3</td>
<td>4.8</td>
</tr>
<tr>
<td>C61</td>
<td>Prostate</td>
<td>3,109</td>
<td>6.2</td>
<td>9.5</td>
</tr>
</tbody>
</table>
Estimated crude incidence rates in 2018, Egypt, females, all ages

- Breast
- Liver
- Non-Hodgkin lymphoma
- Colorectum
- Ovary
- Bladder
- Brain, nervous system
- Thyroid
- Leukaemia
- Corpus uteri

Data source: GLOBOCAN 2018
Graph production: Global Cancer Observatory (http://gco.iarc.fr)

6th
Disease Spectrum

**Histological type**

<table>
<thead>
<tr>
<th>Type</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urothelial 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>&lt;1%</td>
</tr>
</tbody>
</table>

**Bladder Cancer**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superficial</td>
<td>pTa, pTis, pT1</td>
</tr>
<tr>
<td>Muscle-invasive</td>
<td>pT2, pT3, pT4</td>
</tr>
<tr>
<td>Metastatic</td>
<td>N+, M+</td>
</tr>
</tbody>
</table>

**Stage at Diagnosis/5-yrs Survival**

<table>
<thead>
<tr>
<th>Stage at Diagnosis</th>
<th>Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>74% confined to the bladder</td>
<td>93.7%</td>
</tr>
<tr>
<td>19% regional disease</td>
<td>46%</td>
</tr>
<tr>
<td>3% distant metastasis</td>
<td>6.2%</td>
</tr>
</tbody>
</table>
Systemic therapy (neoadjuvant or adjuvant)

Multimodal therapy

Surgery: Radical cystectomy, urinary diversion, lymphadenectomy

Systemic therapy

+/− Palliative RTH

Non-muscle invasive: 70%
Muscle invasive: 25%
Metastatic: 5%

Disease Spectrum
Urothelial Tumours
Overview of Treatment Options

Transurethral resection (TUR)
Intravesical instillations: immunotherapy or chemotherapy
Systemic therapy

Evolution of Systemic Therapy for Urothelial Cancer

- **Publication**
  - Standard MVAC 1989
  - Docetaxel 1997
  - GC 2000
  - Paclitaxel 2002

- **Agency Action**
  - Doxorubicin FDA approved 1974
  - Cisplatin FDA approved 1978
  - Gemcitabine EMA approved 2008
  - Vinflunine EMA approved 2009
  - Pembrolizumab 1st-line cis ineligible May 2017
  - Pembrolizumab 2nd line May 2017
  - Nivolumab 2nd line Feb 2017
  - Atezolizumab 1st-line cis ineligible Apr 2017
  - Durvalumab 2nd line May 2017
  - Avelumab 2nd line May 2017
  - Pembrolizumab 2nd line May 2017
  - Atezolizumab FDA approved 2016
  - Pembrolizumab 2nd line May 2017

- **Timeline**
  - 1974-2017
  - Feb 2017: Nivolumab 2nd line
  - Mar 2017: Atezolizumab 1st-line cis ineligible
  - Apr 2017: Durvalumab 2nd line
  - May 2017: Avelumab 2nd line
  - Feb 2018: Pembrolizumab 2nd line

- **Notes**
  - FDA approved:
    - Cisplatin
    - Doxorubicin
    - Docetaxel
    - Gemcitabine
    - Vinflunine
    - Pembrolizumab
  - EMA approved:
    - Vinflunine

- **References**
  - Doxorubicin FDA approved
  - Cisplatin FDA approved
  - Gemcitabine EMA approved
  - Vinflunine EMA approved

- **Additional Information**
  - Evolution of Systemic Therapy for Urothelial Cancer

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Radical cystectomy is the gold standard for treatment of invasive bladder cancer.

Treatment of muscle invasive bladder cancer

**Urinary Diversion after Radical Cystectomy**

- Orthotopic bladder substitute
  - Both in men and women
  - Except for urethral tumor/positive urethral margin (EG B)

- Fully informed patient about benefits and risks of each type of diversion (EG B)
  - Final decision based on broad consent between patient and treating surgeon

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Indication of Systemic Therapy in M1 Bladder Cancer

- Local Disease
- M1 Bladder Cancer
cT2-T4a and N0 and M0

( RC )
Prior to Radical Local Treatment

Neoadjuvant
Neoadjuvant Cisplatin-based Chemotherapy improves survival in MIBC

Neoadjuvant Cisplatin-based Chemotherapy improves survival in MIBC

10-yr OS:
CMV = 36%
No CMV = 30%

P value: 0.03

Neoadjuvant Cisplatin-based Chemotherapy improves survival in MIBC

Fig. 2. Overall survival curve (platinum based combination chemotherapy trials only).
Efforts to decrease toxicity and improve outcome with MVAC

- GC
- HD MVAC
- DD MVAC
- Accelerated MVAC
Efforts to decrease toxicity with MVAC (GC vs MVAC)

Von der Masse et al., JCO, 2000, 18: 3068
Von der Masse et al., JCO, 2005, 21: 4602
Pathologic complete response as a surrogate for survival

Patients who achieved pCR in the primary tumour and the lymph nodes presented an RR for OS of 0.45 (95% confidence interval [CI], 0.36–0.56; p < 0.00001), Petrelli F et al, Eur Urol, 2014
Neoadjuvant Chemotherapy for Bladder Cancer

**Evidence**
Multiple prospective randomized trials and meta-analyses demonstrate survival advantage from NAC for all eligible patients with MIBC.

**Gap**
1. Only ≈40% of patients with major response appear to benefit from NAC
2. NAC is not widely used in most parts of the world

**Solution**
If we can identify who is likely to respond to NAC and avoid NAC in likely non-responders, we will be able to optimize delivery and increase uptake.
Molecular Predictors of Response to Neoadjuvant Chemotherapy

- Molecular Subtypes
- COXEN Model
- Genomic Alterations
Molecular Predictors of Response to Neoadjuvant Chemotherapy

Molecular Subtypes
Molecular subtypes: basal vs. luminal

Visual Art: © 2014 The University of Texas MD Anderson Cancer Center

David McConkey
Basal tumors most sensitive to neoadjuvant chemo

(non-NAC dataset (n=476) (overall survival) NAC dataset (n=269)

GSC: Seiler, Eur Urol, 2017
UNC: Daumrauer, PNAS, 2014
MDA: Choi, Cancer Cell, 2014

Seiler et al. Eur Urol 2017
Molecular Predictors of Response to Neoadjuvant Chemotherapy

Molecular Subtypes

COXEN Model
SWOG S1314 – “Coxen” Clinical Trial

Biomarker validation and biomarker discovery

Selection Criteria SWOG 8710 (T2-T4a N0M0, cisplatin eligible)

Tumor Sample TURBT

Randomize to chemo

Gem-Cis

MVAC

Cystectomy

Cystectomy Pathology

Validation

Ability of COXEN model to predict pT0 or ≤pT1

Collection

Tissue, blood, urine

Molecular Analysis

Gene expression

Sequencing

microRNA

SNP

Discovery

Collection

Tissue (>P0), blood, urine

Molecular Analysis

Gene expression

Sequencing

microRNA

SNP

Tom Flaig

Dan Theodorescu
Molecular Predictors of Response to Neoadjuvant Chemotherapy

- Molecular Subtypes
- COXEN Model
- Genomic Alterations
ERCC2 Mutations: Validation

![Graph showing overall survival for ERCC2 mutation and no ERCC2 mutation cohorts.]

No. at risk by time
No ERCC2 mutation 38
ERCC2 mutation 10

Overall Survival, d

Proportion Surviving

0.0 0.2 0.4 0.6 0.8 1.0
0 500 1000 1500

P = .03

Cancer Discovery October 2014

Liu et al JAMA Oncol 2016
Mutations in ATM, RB1, FANCC

Overall survival

**A**
- Progression-free survival (%)
- Discovery (AMVAC)
- \( p = 0.0085 \)
- ATM/RB1/FANCC wt
- ATM/RB1/FANCC mut
- \# PTs at risk
  - wt: 21, 16, 12, 6, 2
- Time (mo)

**B**
- Progression-free survival (%)
- Validation (DDGC)
- \( p = 0.102 \)
- ATM/RB1/FANCC wt
- ATM/RB1/FANCC mut
- \# PTs at risk
  - wt: 15, 9, 4, 0
- Time (mo)

---

**Discovery:** dose-dense MVAC

**Validation:** dose-dense Gem-Cis

Plimack et al Eur Urol 2015
Where do these markers leave us?

- Basal subtype of bladder cancer appears to benefit most from neo-adjuvant chemotherapy.
- COXEN model predicts response to neoadjuvant chemo in individual patient.
- Alterations in DNA repair genes may allow for enrichment of likely responders.
- All of this needs to be validated in trials.
Neoadjuvant Therapy for MIBC

Eligible for cisplatin-based therapy

Gemcitabine + Cisplatin or ddMVAC → Cystectomy

Ineligible for cisplatin-based therapy

Cystectomy
Integrating CPI into Neoadjuvant Therapy

- Single Agent
- CPI Doublets
- Chemo + CPI
ABACUS and PURE-01: Phase II Trials of Neoadjuvant Checkpoint Inhibition Muscle Invasive Bladder Cancer

**ABACUS:**
Atezolizumab
1200 mg Q3W x 2 doses
(N = 95)¹

**PURE-01:**
Pembrolizumab
200 mg Q3W x 3 doses
(N = 50)²

Cystectomy

pCR Rate With PD-1/PD-L1 Blockade Similar to Cisplatin-Based NAC

pCR Rate With PD-1/PD-L1 Blockade Similar to Cisplatin-Based NAC

ABACUS: Survival Based on pCR Status Following Neoadjuvant Atezolizumab

Does achieving pCR with neoadjuvant PD-1/PD-L1 blockade correlate with improved long-term outcomes?

KEYNOTE-905: Pembrolizumab + Cystectomy vs Cystectomy in Cisplatin-Ineligible Patients With MIBC

- Multicenter, randomized phase III trial

  Multicenter, randomized phase III trial

  

  PD-L1 (CPS ≥ 10% or < 10%), disease stage, and geographic region

  Cisplatin-ineligible pts with stage T2-T4aN0M0 MIBC; predominant urothelial histology; ECOG PS 0-2; no previous systemic therapy for MIBC (Planned N = 610)

  Pembrolizumab
  
  
  200 mg Q3W for 3 cycles

  Cystectomy + PLND

  Pembrolizumab
  
  
  200 mg Q3W for up to 14 cycles

  Cystectomy + PLND

  Best supportive care (adjuvant CT if indicated)

  Crossover to pembrolizumab allowed at PD

- Primary endpoint: pCR and EFS (in PD-L1 CPS ≥ 10% and ITT populations)

- Key secondary endpoint: OS (in PD-L1 CPS ≥ 10% and ITT populations)

Early Phase Studies of Neoadjuvant Doublet CPI Therapy in MIBC

NCT02812420  
Durvalumab + treemelimumab x 2\(^1\)

NABUCCO  
Ipilimumab + nivolumab x 3\(^2\)

Cystectomy

**Summary: Neoadjuvant Systemic Therapy of Bladder Cancer**

<table>
<thead>
<tr>
<th>Neoadjuvant</th>
<th>Preferred</th>
<th>Alternate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin eligible</td>
<td>Cis Gem or DD MVAC</td>
<td>Checkpoint inhibitor on a clinical trial</td>
</tr>
<tr>
<td>Cisplatin ineligible</td>
<td>Upfront surgery, then consider adjuvant trial</td>
<td>Checkpoint inhibitor on a clinical trial</td>
</tr>
</tbody>
</table>

*Consider testing for PD-L1 using the appropriate companion diagnostic and limiting treatment to those who are PD-L1 positive*
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- Local Disease
- MI Bladder Cancer
  - cT2-T4a and N0 and M0

Radical Cystectomy

After Radical Local Treatment

Adjuvant
**Guidelines**

<table>
<thead>
<tr>
<th>EAU</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Offer adjuvant cisplatin-based combination chemotherapy to patients with pT3/4 and/or pN+ disease if no neoadjuvant chemotherapy has been given.</td>
<td>C</td>
</tr>
</tbody>
</table>

**Flowchart**

- **ESMO**
  - Muscle Invasive
    - Neoadjuvant Chemotherapy
      - Radical Cystectomy with Lymphadenectomy
        - Further Adjuvant Chemotherapy (limited data)
        - Adjuvant Chemotherapy (if no neoadjuvant)
      - Every three months follow up (see text)
# Adjuvant Chemotherapy

**DFS**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skinner 1991</td>
<td>-0.3147</td>
<td>0.2247</td>
<td>12.7%</td>
<td>0.73 [0.47, 1.13]</td>
<td>1991</td>
<td></td>
</tr>
<tr>
<td>Studer 1994</td>
<td>0.0198</td>
<td>0.288</td>
<td>10.5%</td>
<td>1.02 [0.58, 1.79]</td>
<td>1994</td>
<td></td>
</tr>
<tr>
<td>Freinha 1996</td>
<td>-0.7765</td>
<td>0.3537</td>
<td>8.7%</td>
<td>0.46 [0.23, 0.92]</td>
<td>1996</td>
<td></td>
</tr>
<tr>
<td>Bono 1997</td>
<td>-0.2877</td>
<td>0.3081</td>
<td>9.9%</td>
<td>0.75 [0.41, 1.37]</td>
<td>1997</td>
<td></td>
</tr>
<tr>
<td>Lehmann 2006</td>
<td>-1.0498</td>
<td>0.3393</td>
<td>9.0%</td>
<td>0.35 [0.18, 0.68]</td>
<td>2006</td>
<td></td>
</tr>
<tr>
<td>Paz-Ares 2010</td>
<td>-0.9676</td>
<td>0.2136</td>
<td>13.1%</td>
<td>0.38 [0.25, 0.58]</td>
<td>2010</td>
<td></td>
</tr>
<tr>
<td>Stadler 2011</td>
<td>-0.0202</td>
<td>0.4086</td>
<td>7.3%</td>
<td>0.98 [0.44, 2.18]</td>
<td>2011</td>
<td></td>
</tr>
<tr>
<td>Cognetti 2012</td>
<td>0.077</td>
<td>0.1998</td>
<td>13.6%</td>
<td>1.08 [0.73, 1.60]</td>
<td>2012</td>
<td></td>
</tr>
<tr>
<td>Stemberg 2015</td>
<td>-0.6162</td>
<td>0.1531</td>
<td>15.2%</td>
<td>0.54 [0.40, 0.73]</td>
<td>2015</td>
<td></td>
</tr>
</tbody>
</table>

**Total (95% CI)**

- Heterogeneity: Tau² = 0.11; Chi² = 22.39, df = 8 (P = 0.004); I² = 64%
- Test for overall effect: Z = 3.08 (P = 0.002)

**OS**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skinner 1991</td>
<td>-0.2877</td>
<td>0.2727</td>
<td>13.5%</td>
<td>0.75 [0.48, 1.17]</td>
<td>1991</td>
<td></td>
</tr>
<tr>
<td>Studer 1994</td>
<td>0.0198</td>
<td>0.2969</td>
<td>7.9%</td>
<td>1.02 [0.57, 1.83]</td>
<td>1994</td>
<td></td>
</tr>
<tr>
<td>Freinha 1996</td>
<td>-0.2485</td>
<td>0.3945</td>
<td>4.5%</td>
<td>0.78 [0.36, 1.69]</td>
<td>1996</td>
<td></td>
</tr>
<tr>
<td>Bono 1997</td>
<td>-0.4308</td>
<td>0.3306</td>
<td>6.4%</td>
<td>0.65 [0.34, 1.24]</td>
<td>1997</td>
<td></td>
</tr>
<tr>
<td>Otto 2001</td>
<td>-0.1985</td>
<td>0.2732</td>
<td>9.3%</td>
<td>0.82 [0.48, 1.40]</td>
<td>2001</td>
<td></td>
</tr>
<tr>
<td>Lehmann 2006</td>
<td>-0.5821</td>
<td>0.3108</td>
<td>7.2%</td>
<td>0.57 [0.31, 1.05]</td>
<td>2006</td>
<td></td>
</tr>
<tr>
<td>Paz-Ares 2010</td>
<td>-0.9676</td>
<td>0.2789</td>
<td>9.0%</td>
<td>0.38 [0.22, 0.66]</td>
<td>2010</td>
<td></td>
</tr>
<tr>
<td>Stadler 2011</td>
<td>0.1044</td>
<td>0.4607</td>
<td>3.3%</td>
<td>1.11 [0.45, 2.74]</td>
<td>2011</td>
<td></td>
</tr>
<tr>
<td>Cognetti 2012</td>
<td>0.2546</td>
<td>0.2189</td>
<td>14.6%</td>
<td>1.29 [0.84, 1.98]</td>
<td>2012</td>
<td></td>
</tr>
<tr>
<td>Stemberg 2015</td>
<td>-0.2485</td>
<td>0.1691</td>
<td>24.4%</td>
<td>0.78 [0.56, 1.09]</td>
<td>2015</td>
<td></td>
</tr>
</tbody>
</table>

**Total (95% CI)**

- Heterogeneity: Chi² = 14.71, df = 9 (P = 0.10); I² = 39%
- Test for overall effect: Z = 2.90 (P = 0.004)

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Kim HS et al, 2017, Oncotarget, 8 (46):81204-81214
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- MI Bladder Cancer
  - cT2-T4a and N0 and M0

Radical Radiotherapy

With Radical Local Treatment
  - Concurrent
Is it possible to conserve the bladder?
Organ preservation therapy

- Indications:
  - Pts refusing Sx
  - Pts unfit for Sx

- Protocol utilize:
  - Tri-modality combination of TURBT plus radiotherapy and chemotherapy.
Radiotherapy with or without Chemotherapy in Muscle-Invasive Bladder Cancer

RT: 55 Gy / 20 # or 64 Gy / 32 #
ChT: Mitomycin / 5FU

458 patients
CYSTECTOMY RATE = 10%

James et al. NEJM 2012
Typical schema for bladder CMT

1. TURBT
2. XRT (40Gy) + Concomitant Chemotherapy
3. Cystoscopic response evaluation
   - CR
   - Non-CR

   - Consolidation Chemo-radiation (64Gy)
   - Frequent cystoscopy

   - Radical cystectomy
## Multimodality Treatment for MIBC

<table>
<thead>
<tr>
<th>Series (Ref.)</th>
<th>Multimodality Therapy Used</th>
<th>No. of Patients</th>
<th>5-Year Overall Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTOG 8512, 1993 (74)</td>
<td>External-beam radiation with cisplatin</td>
<td>42</td>
<td>52</td>
</tr>
<tr>
<td>RTOG 8802, 1996 (75)</td>
<td>TURBT, MCV, external-beam radiation with cisplatin</td>
<td>91</td>
<td>51</td>
</tr>
<tr>
<td>RTOG 8903, 1998 (76)</td>
<td>TURBT with or without MCV, external-beam radiation with cisplatin</td>
<td>123</td>
<td>49</td>
</tr>
<tr>
<td>U. Paris, 1997 (77)</td>
<td>TURBT, 5-FU, external-beam radiation with cisplatin</td>
<td>120</td>
<td>63</td>
</tr>
<tr>
<td>Erlangen, 2002 (78)</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>50</td>
</tr>
<tr>
<td>RTOG 9906 (79)</td>
<td>TURBT, TAX plus CP plus XRT; adj. CP plus GEM</td>
<td>80</td>
<td>56</td>
</tr>
<tr>
<td>MGH, 2009 (80)</td>
<td>TURBT, external beam radiation and cisplatin with or without 5-FU or TAX; neoadj. or adj. chemotherapy</td>
<td>348</td>
<td>52</td>
</tr>
</tbody>
</table>
Pooled analysis (N = 468) of long-term outcomes from RTOG studies of combined-modality therapy for muscle-invasive bladder cancer

- Phase II: RTOG 8802, 9506, 9706, 9906, and 0233
- Phase III: RTOG 8903

Pooled Analysis of Long-term Outcomes in MIBC After Bladder-Preserving CMT

- Long-term outcomes with bladder-preserving CMT comparable to outcomes reported for previous single-institution series
- Decreased OS, DSS associated with higher clinical stage
- Improved DSS associated with complete response to CMT

<table>
<thead>
<tr>
<th>Clinical Stage, %</th>
<th>OS (P = .002)</th>
<th>DSS (P = .05)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 Yr</td>
<td>10 Yr</td>
</tr>
<tr>
<td>T2</td>
<td>62</td>
<td>41</td>
</tr>
<tr>
<td>T3/T4</td>
<td>49</td>
<td>30</td>
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</tbody>
</table>

Guidelines for Multimodality Treatment
Organ Preservation Therapy (cystectomy ineligible, patient preference)

TURBT (should aim for complete)

Combined chemoradiotherapy 40 Gy

Combined chemoradiotherapy Total dose 55-64 Gy

Radiotherapy alone

Imaging + TURBT evaluation

Salvage cystectomy if persisting tumour

Complete Radiotherapy if complete response (CR)

Surveillance Cystoscopic evaluation (3 months) with TUR bladder biopsy (every 6 months)
NCCN Guidelines Version 1.2020
Muscle Invasive Bladder Cancer

**CLINICAL ADDITIONAL WORKUP**

- Abdominal/pelvic CT or MRI if not previously done
- Chest imaging
- Bone scan if clinical suspicion or symptoms of bone metastases

**STAGING**

- Stage II (cT2, N0)

**PRIMARY TREATMENT**

- Neoadjuvant cisplatin-based combination chemotherapy followed by radical cystectomy (category 1)
- Neoadjuvant cisplatin-based combination chemotherapy followed by partial cystectomy (highly selected patients with solitary lesion in a suitable location; no Tis)

**Cystectomy candidates**

- Cystectomy alone for those not eligible to receive cisplatin-based chemotherapy
- Concurrent chemoradiotherapy (category 1)

**Non-cystectomy candidates**

- See BL-6

**ADJUVANT TREATMENT**

- Based on pathologic risk (pT3-4 or positive nodes or positive margins), consider adjuvant cisplatin-based chemotherapy or consider adjuvant RT (category 2B) if no neoadjuvant treatment given

- See Follow-up (BL-E)

- No tumor → Observation
- Tumor → Surgical consolidation or treat as metastatic disease (BL-10)

- Reassessment tumor status 2-3 months after full treatment
Which Chemotherapy to give?

Chemotherapy regimens

- Cisplatin with 5-fluorouracil (RTOG 0233; RTOG 9506)
- Paclitaxel with cisplatin (RTOG 9906)
- Cisplatin alone 100 mg/m² q 2 weeks x3
- Weekly gemcitabine 75-100 mg/m²
- Twice weekly gemcitabine 27 mg/m² (RTOG 0712)
Organ Preservation Therapy

- Reasonable alternative
- Contemporary treatment involves:
  - Maximal TURBT
  - Concomitant chemoRT
- Patient selection important
  - Visibly complete TURBT
  - Tumor <5 cm
  - No or minimal Tis
  - No hydronephrosis
  - No evidence of nodal disease
  - Adequate bladder capacity and function
Systemic Therapy Update in the Management of Bladder Cancer

- Introduction
- Neoadjuvant systemic therapy
- Adjuvant systemic therapy
- Multimodality therapy and organ preservation
- Treatment of advanced/metastatic disease
EAU–ESMO consensus statements on the management of advanced and variant bladder cancer—an international collaborative multi-stakeholder effort: under the auspices of the EAU and ESMO Guidelines Committees†

<table>
<thead>
<tr>
<th>Speciality</th>
<th>Round 1, N</th>
<th>Round 2, N</th>
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</thead>
<tbody>
<tr>
<td>Urology</td>
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<td>Oncology</td>
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<td>Medical Oncology</td>
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<td>Radiation Oncology</td>
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<tr>
<td>Other</td>
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<td>Nuclear Medicine</td>
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<td>Radiology</td>
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<td>Specialist nurse</td>
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<td>Clinical Oncology</td>
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<td>Total</td>
<td>113</td>
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Table 12. Consensus meeting statements regarding ICIs in urothelial bladder cancer

<table>
<thead>
<tr>
<th>Proposed statements</th>
<th>Level of agreement</th>
<th>N</th>
<th>Consensus achieved</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Pseudo-progression has not been demonstrated in urothelial cancer</td>
<td>Disagree (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. In contrast to the first-line setting, the PD-L1 biomarker is not useful for</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>selecting patients for immunotherapy in platinum-refractory metastatic urothelial</td>
<td>Equivocal (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Carboplatin-based chemotherapy remains a viable first-line treatment option</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>in cisplatin-ineligible, PD-L1-positive patients with metastatic urothelial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>carcinoma until data from randomised phase III trials of ICIs are available</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Cisplatin-ineligible, immunotherapy-refractory patients with metastatic</td>
<td></td>
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<td></td>
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<tr>
<td>urothelial carcinoma should be considered for chemotherapy instead of</td>
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</tr>
<tr>
<td>sequencing of immunotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

|                                  | Agree (%) |     |                   |
|                                  | 89        | 28  | Yes               |
|                                  | 81        | 28  | Yes               |
|                                  | 87        | 29  | Yes               |
|                                  | 81        | 27  | Yes               |
**PRINCIPLES OF SYSTEMIC THERAPY**

Second-line systemic therapy for locally advanced or metastatic disease (Stage IV) (post-platinum)\(^c\)

<table>
<thead>
<tr>
<th>Preferred regimen</th>
<th>Other recommended regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Pembrolizumab (category 1)(^{18})</td>
<td>• Paclitaxel(^{26}) or docetaxel(^{27})</td>
</tr>
<tr>
<td>• Atezolizumab(^{19,20})</td>
<td>• Gemcitabine(^{14})</td>
</tr>
<tr>
<td>• Nivolumab(^{21})</td>
<td></td>
</tr>
<tr>
<td>• Durvalumab(^{22})</td>
<td></td>
</tr>
<tr>
<td>• Avelumab(^{23,24})</td>
<td></td>
</tr>
<tr>
<td>• Erdafitinib(^{d,25})</td>
<td></td>
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</tbody>
</table>

Alternative preferred regimens

<table>
<thead>
<tr>
<th>Preferred regimen</th>
<th>Other recommended regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Immune checkpoint inhibitor</td>
<td>Useful in certain circumstances based on prior medical therapy</td>
</tr>
<tr>
<td>› Atezolizumab(^{19,20})</td>
<td>• Ifosfamide, doxorubicin, and gemcitabine(^{16})</td>
</tr>
<tr>
<td>› Nivolumab(^{21})</td>
<td>• Gemcitabine and paclitaxel(^{15})</td>
</tr>
<tr>
<td>› Durvalumab(^{22})</td>
<td>• Gemcitabine and cisplatin(^{4})</td>
</tr>
<tr>
<td>› Avelumab(^{23,24})</td>
<td>• DDMVAC with growth factor support(^{2})</td>
</tr>
<tr>
<td>• Erdafitinib(^{d,25})</td>
<td></td>
</tr>
</tbody>
</table>

Second-line systemic therapy for locally advanced or metastatic disease (Stage IV) (post-checkpoint inhibitor)

<table>
<thead>
<tr>
<th>Preferred regimen for cisplatin ineligible, chemotherapy naïve</th>
<th>Other recommended regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Gemcitabine/carboplatin</td>
<td>• Erdafitinib(^{d,25})</td>
</tr>
<tr>
<td></td>
<td>• Paclitaxel or docetaxel(^{27})</td>
</tr>
<tr>
<td></td>
<td>• Gemcitabine(^{14})</td>
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</tbody>
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<table>
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<tr>
<th>Preferred regimens for cisplatin eligible, chemotherapy naïve</th>
<th>Useful in certain circumstances based on prior medical therapy</th>
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<tr>
<td>• Gemcitabine and cisplatin(^{4})</td>
<td>• Ifosfamide, doxorubicin, and gemcitabine(^{16})</td>
</tr>
<tr>
<td>• DDMVAC with growth factor support(^{2})</td>
<td>• Gemcitabine and paclitaxel(^{15})</td>
</tr>
</tbody>
</table>
Some Future and ongoing clinical trials
Key first-line Phase III trials of anti-PD-1/PD-L1 antibodies in urothelial cancer

NCT02807636 (IMvigor130): N=1,200
- First-line cisplatin-ineligible, locally advanced/metastatic
- ECOG PS ≤2

Co-primary endpoints: PFS, OS and safety

NCT02516241 (DANUBE): N=1,005
- First-line unresectable stage IV
- Eligible/ineligible for cisplatin-based chemotherapy

Co-primary endpoints: PFS and OS

NCT02853305 (KEYNOTE-361): N=990
- First-line unresectable or metastatic
- ECOG PS ≤2

Co-primary endpoints: PFS and OS

NCT03036098 (CheckMate-901): N=897
- First-line unresectable or metastatic
- ECOG PS ≤1

Co-primary endpoints: PFS and OS

- ECOG PS: Eastern Cooperative Oncology Group performance status; OS, overall survival; PD-1, programmed death-1; PD-L1, programmed death ligand-1; PFS, progression-free survival.

Metastatic UBC: New Drug Approvals 1995-20

Systemic therapy in bladder cancer

We are in a new era!

Financial Toxicity : A New Term
Thanks For Your Attention