Combined Modality Management for Bladder Cancer

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Radiation Oncology cCARE
Introduction

- Most common malignancy involving the urinary system
  - ~80,000 new cases and 18,000 deaths in US each year
- Occurs more frequently in men, Caucasians and older adults
- 70% diagnosed bladder cancers start at an early stage, but may recur even with treatment
- Other parts of the urinary tract at risk
Introduction

• Causes include:
  • Smoking / tobacco use
  • Exposure to chemicals (i.e. arsenic, dye manufacturing, rubber, leather, textiles, paint, cyclophosphamide)
  • Prior radiation exposure
  • Chronic irritation of the bladder lining (infections or inflammation)
  • Parasitic infection, particularly outside of the US
  • Association with increased intake of stewed / roasted meat (but reduced risk associated with high intake of vegetables and milk/yogurt); Crippa Eur J Nutr 2019

• Clinical Presentation
  • Classically presents with painless hematuria (gross or microscopic)
  • Pain typically associated with locally advanced or metastatic tumors
If muscle-invasive:
- CT AP or MRI
- Chest imaging
- Bone scan if suspicion of bone metastases
Pathology

- Urothelial (transitional cell) carcinoma account for 90% in US and Europe
- Squamous cell carcinoma
  - ~75% in other part of the world where Schistosomo haematobium infection is endemic
- Adenocarcinoma
- Small cell carcinoma

http://phil.cdc.gov/
Staging

AJCC 8th Edition

<table>
<thead>
<tr>
<th>T</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ta</td>
<td>Noninvasive papillary carcinoma</td>
</tr>
<tr>
<td>Tis</td>
<td>Urothelial carcinoma in situ: “Flat tumor”</td>
</tr>
<tr>
<td>T1</td>
<td>Invades lamina propria (subepithelial connective tissue)</td>
</tr>
<tr>
<td>T2</td>
<td>Invades muscularis propria</td>
</tr>
<tr>
<td>T2a</td>
<td>Superficial (inner half)</td>
</tr>
<tr>
<td>T2b</td>
<td>Deep (outer half)</td>
</tr>
<tr>
<td>T3</td>
<td>Invades perivesical soft tissue</td>
</tr>
<tr>
<td>T3a</td>
<td>Microscopically</td>
</tr>
<tr>
<td>T3b</td>
<td>Macroscopically</td>
</tr>
<tr>
<td>T4</td>
<td>Direct invasion of prostatic stroma, seminal vesicles, uterus, vagina (T4a),</td>
</tr>
<tr>
<td></td>
<td>pelvic wall, abdominal wall (T4b)</td>
</tr>
</tbody>
</table>

Diagram showing layers of tissue including Fat, Muscle, Connective tissue, Bladder lining, CIS, Ta, T1, T2, T3, T4.
# Staging

**AJCC 8th Edition**

<table>
<thead>
<tr>
<th>N</th>
<th>N1 – Single regional LN true pelvis (perivesical, obturator, int/ext iliac, sacral)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N2 – Multiple regional LN in true pelvis</td>
</tr>
<tr>
<td></td>
<td>N3 – Common iliac LN</td>
</tr>
<tr>
<td>M</td>
<td>M1 – Distant metastasis</td>
</tr>
<tr>
<td></td>
<td>M1a  Limited to LN beyond common iliacs</td>
</tr>
<tr>
<td></td>
<td>M1b  Non-LN DM</td>
</tr>
</tbody>
</table>

Mao Current Rad Report 2014
### AJCC 8th Edition

<table>
<thead>
<tr>
<th>Stage</th>
<th>T (Primary)</th>
<th>N (Regional)</th>
<th>M (Distant)</th>
<th>Staging / Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ta Tis</td>
<td>0a 0is</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>N0 M0</td>
<td></td>
<td></td>
<td>I</td>
</tr>
<tr>
<td>T2</td>
<td>N0 M0</td>
<td></td>
<td></td>
<td>II</td>
</tr>
<tr>
<td>T3-4a</td>
<td>N0 M0</td>
<td></td>
<td></td>
<td>IIIA</td>
</tr>
<tr>
<td>T1-4a</td>
<td>N1 M0</td>
<td></td>
<td></td>
<td>IIIB</td>
</tr>
<tr>
<td>T1-4a</td>
<td>N2-3 M0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4b</td>
<td>Any N M0</td>
<td>Any M1a</td>
<td>IVA</td>
<td>IVA</td>
</tr>
<tr>
<td>Any T</td>
<td>Any N</td>
<td>M1b</td>
<td>IVB</td>
<td></td>
</tr>
</tbody>
</table>

### 5-year relative survival rates for bladder cancer

(Based on people diagnosed with bladder cancer between 2008 and 2014.)

<table>
<thead>
<tr>
<th>SEER Stage</th>
<th>5-year Relative Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized</td>
<td>69%</td>
</tr>
<tr>
<td>In situ alone</td>
<td>95%</td>
</tr>
<tr>
<td>Regional</td>
<td>35%</td>
</tr>
<tr>
<td>Distant</td>
<td>5%</td>
</tr>
<tr>
<td>All SEER stages combined</td>
<td>77%</td>
</tr>
</tbody>
</table>
Treatment

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Bladder Cancer

NCCN Evidence Blocks™

NCCN Guidelines Version 4.2019
Bladder Cancer
NCCN Evidence Blocks™

Non-Muscle Invasive

CLINICAL STAGINGd,e,f  SECONDARY SURGICAL TREATMENT  ADJUVANT INTRAVESICAL TREATMENTh,i  FOLLOW-UPa

- cT1a, low grade
  - Observation or Intravesical chemotherapyj
  - See Follow-up (BL-E)

- cT1a, high grade
  - If incomplete resection, repeat TURBT
  - If no muscle in specimen, strongly consider repeat TURBT
  - BCG (preferred) or Intravesical chemotherapyj
  - Observation

- cT1, low grade
  - Strongly advise repeat TURBT or Consider cystectomyk,lg for high-grade
  - Residual disease
    - BCG (category 1) or Cystectomyk,lg
  - No residual disease
    - BCG (preferred) (category 1) or Intravesical chemotherapyj
      - Observation in highly selected casesm

- cT1, high grade
  - BCG

- Any Tis
  - BCG
Treatment

• Muscle-invasive (i.e. T2)
  • Cystectomy candidate
    • **Surgical approach**
      • Neoadjuvant cisplatin-based combo chemotherapy f/b radical cystectomy (cat 1)
      • Neoadjuvant cisplatin-based combo chemotherapy f/b partial cystectomy if suitable location
      • Cystectomy alone if not eligible for cisplatin-based chemotherapy
    • **Non-surgical approach**
      • Concurrent chemoradiation (cat 1) aka bladder preservation
  • Non-cystectomy candidate
    • Concurrent chemoradiation or RT alone
    • TURBT and consider intravesical BCG

• Node positive or M1a (LN only metastasis)
  • Consider downstaging systemic therapy first vs concurrent chemoradiation
  • Consider postop adjuvant RT or chemotherapy if pT3-4 or N+

• M1b (Distant mets)
  • Systemic therapy
Neoadjuvant / Preoperative chemotherapy

- Neoadjuvant cisplatin-based combination regimens have showed a survival benefit when given prior to surgery
  - Advanced Bladder Cancer Meta-analysis Collaboration Lancet 2003
    - 2688 pts from 10 randomized trials:
      - 13% reduction in risk of death, 5% absolute benefit at 5 years (OS increased from 45-50%)
      - Lower risk of recurrence with absolute DFS 7%
  - BA06 30894 Griffiths 2011
    - 976 pts (1989-1995) given neoadjuvant CMV before definitive surgery vs RT
      - Metastasis-free survival 23 vs 33% p, OS 30 vs 36% p

- Different neoadjuvant regimens have not been compared in randomized trials

- Common regimens:
  - Classic MVAC (methotrexate, vinblastine, doxorubicin, cisplatin)
  - Dose-dense MVAC
  - Gemcitabine + cisplatin
  - CMV (methotrexate, vinblastine, cisplatin, leucovorin)
Cystectomy vs bladder preservation

- No completed randomized studies comparing radical cystectomy and bladder preservation approaches
  - Multiple series suggest favorable results in well-selected patients with bladder preservation

- SPARE: Selective bladder preservation against radical excision
  - UK trial
  - Closed 2010 due to poor accrual
Bladder preservation approach

Figure 65.3 Schema for trimodality treatment of muscularis propria-invasive bladder cancer with selective bladder preservation. XRT, radiation therapy.

(Diagram edited by speaker for slide)
**Irradiated bowel & urinary diversion**

- **Neobladder**
  - Sphere-shaped reservoir created from intestine, attached to urethra
  - Normal urination possible, intermittent catherization sometimes needed if difficulty emptying

- **Ileal conduit**
  - Tube created from intestine connected to ureters to outside the body into urostomy bag

- **Continent urinary reservoir**
  - Small pouch / reservoir made from intestine to hold urine, then drained through opening in the abdomen with intermittent catheterization
Concurrent chemoradiation vs RT alone

- NCIC (Coppin 1996)
  - 1985-1989; 99 patients cT2-T4b (mostly cT3-4)
  - RT alone vs with concurrent cisplatin
    - RT: preop vs definitive decided prior to enrollment
Concurrent chemoradiation vs RT alone

- NCIC (Coppin 1996)

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Pelvic failure</td>
<td>5y: 59 vs 40% p</td>
</tr>
<tr>
<td></td>
<td>As first site of failure: 52 vs 29%</td>
</tr>
<tr>
<td>Distant mets</td>
<td>No difference</td>
</tr>
<tr>
<td>OS</td>
<td>3y: 33% vs 47% NS</td>
</tr>
<tr>
<td>Bladder presv.</td>
<td>36% vs 70% ns</td>
</tr>
</tbody>
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- Critique: Underpowered
Concurrent chemoradiation vs RT alone

- **BC2001 (CRUK / 01 / 004)**
  - Phase III: RT +/- synchronous 5FU and MMC
  - Also had RT specific randomizations
  - 2001-2008: 360 pts with cT2-T4aN0
  - James NEJM 2012

- C+RT significantly improved locoregional control

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<tbody>
<tr>
<td>RFS</td>
<td>2y 67% vs 54% p</td>
</tr>
<tr>
<td>LRR</td>
<td>2y 18% vs 32% (mostly due to ↓ recurrent muscle-invasive)</td>
</tr>
</tbody>
</table>

Low incidence pelvic relapse in both arms

OS 5y 48% vs 35% NS but curves diverge after 2y

↑ Toxicities w chemo but no difference in late tox
Concurrent Chemotherapy

- Cisplatin-based regimen favored (cisplatin and 5FU or cisplatin and paclitaxel) in North America
- Other options include FU plus MMC or single agent paclitaxel
- Carboplatin possibly not as effective
- Gemcitabine may be used as alternative to cisplatin
Bladder preservation

- Retrospective series from Massachusetts General Hospital Experience
  - Giacalone Eur Urol 2017
  - 1986 to 2013; 475 patients with cT2-T4a N0M0 MIBC treated on or per protocols
    - TURBT f/b concurrent CRT, then evaluation and rebiopsy
    - → if CR, completed CCRT but if <CR or invasive recurrence, recommended salvage radical cystectomy

Table 1 – Protocol design and treatment

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Neoadjuvant chemotherapy</th>
<th>Induction</th>
<th>Response</th>
<th>Consolidation or cystectomy</th>
<th>Maximum RT dose to tumor (Gy)</th>
<th>Adjuvant chemotherapy</th>
<th>Pt., n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MGH 180</td>
<td>MCV</td>
<td>2 cycles</td>
<td>CR</td>
<td>CR</td>
<td>64.8</td>
<td>None</td>
<td>52 (11)</td>
</tr>
<tr>
<td>MGH 880, RTOG 8903 Arm 1</td>
<td>MCV</td>
<td>2 cycles</td>
<td>IR</td>
<td>Cystectomy</td>
<td>64.8</td>
<td>None</td>
<td>50 (12)</td>
</tr>
<tr>
<td>MGH 880, RTOG 8903 Arm 2</td>
<td>None</td>
<td>CR</td>
<td>CR</td>
<td>Cystectomy</td>
<td>64.8</td>
<td>None</td>
<td>50 (11)</td>
</tr>
<tr>
<td>MGH 930A</td>
<td>None</td>
<td>CP + 5-FU + BID RT</td>
<td>IR</td>
<td>Cystectomy</td>
<td>64.8</td>
<td>MCV</td>
<td>21 (44)</td>
</tr>
<tr>
<td>RTOG 9506</td>
<td>None</td>
<td>CP + 5-FU + BID RT</td>
<td>CR</td>
<td>Cystectomy</td>
<td>44</td>
<td>None</td>
<td>15 (3.2)</td>
</tr>
<tr>
<td>KUG 9/06</td>
<td>None</td>
<td>CP + BID RT</td>
<td>IR</td>
<td>Cystectomy</td>
<td>64.8</td>
<td>MCV</td>
<td>25 (4.8)</td>
</tr>
<tr>
<td>RTOG 9506</td>
<td>None</td>
<td>CP + pacl + BID RT</td>
<td>CR</td>
<td>Cystectomy</td>
<td>64.3</td>
<td>CP + gem</td>
<td>44 (9.3)</td>
</tr>
<tr>
<td>RTOG 0233 Arm 1</td>
<td>None</td>
<td>CP + 5-FU + BID RT</td>
<td>IR</td>
<td>Cystectomy</td>
<td>64.3</td>
<td>CP + Pacl + gem</td>
<td>28 (5.9)</td>
</tr>
<tr>
<td>RTOG 0233 Arm 2</td>
<td>None</td>
<td>CP + Pacl + BID RT</td>
<td>IR</td>
<td>Cystectomy</td>
<td>64.3</td>
<td>CP + Pacl + gem</td>
<td>33 (6.9)</td>
</tr>
<tr>
<td>RTOG 0524 Group 2</td>
<td>None</td>
<td>Pacl + QD RT</td>
<td>CR</td>
<td>Cystectomy</td>
<td>64.8</td>
<td>None</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>RTOG 0712 Arm 1</td>
<td>None</td>
<td>CP + 5-FU + BID RT</td>
<td>CR</td>
<td>Cystectomy</td>
<td>64.3</td>
<td>CP + gem</td>
<td>18 (1.8)</td>
</tr>
<tr>
<td>RTOG 0712 Arm 2</td>
<td>None</td>
<td>Gem + QD RT</td>
<td>IR</td>
<td>Cystectomy</td>
<td>64</td>
<td>CP + gem</td>
<td>14 (2.9)</td>
</tr>
<tr>
<td>Per protocol</td>
<td>Varied*</td>
<td>Varied*</td>
<td>IR</td>
<td>Cystectomy</td>
<td>64–88</td>
<td>Varied*</td>
<td>118 (25)</td>
</tr>
</tbody>
</table>
Bladder preservation

- Median f/u was 7.21 years
- Response to induction
  - 75% had CR
  - Better CR rate with visibly complete TURBT (84% vs 58%, p<0.0001)
- One cystectomy for treatment-related toxicity (cystitis, persistent hematuria)

<table>
<thead>
<tr>
<th></th>
<th>5 year</th>
<th>10 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSS</td>
<td>66%</td>
<td>59%</td>
</tr>
<tr>
<td>OS</td>
<td>57%</td>
<td>39%</td>
</tr>
</tbody>
</table>

Risk of salvage cystectomy:
- 29% at 5y
- 31% at 10y

129 required salvage cystectomy:
- 65 immediate for <CR
- 64 on surveillance [Median 1.6y (0.3-2.4)]
**Bladder preservation**

- MVA predictors for OS and DSS:
  - T2 disease
  - CR
  - Presence of tumor-associated CIS
  - (OS: Presence of hydronephrosis)

- Improvement over time:

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>66%</td>
<td>88%</td>
</tr>
<tr>
<td>5y DSS</td>
<td>60%</td>
<td>84%</td>
</tr>
<tr>
<td>5y salvage cystectomy</td>
<td>42%</td>
<td>16%</td>
</tr>
<tr>
<td>5y Bladder-intact DSS</td>
<td>40%</td>
<td>75%</td>
</tr>
</tbody>
</table>
Fig. 2 - (A) Improvements in overall survival, (B) disease-specific survival, and (C) bladder-intact disease-specific survival, with (D) a reduction in the crude rate of salvage cystectomy over three treatment eras.
**Contraindications to bladder preservation**

- Tumor >4-5cm
- Tumor associated hydronephrosis / ureter
- Multifocal tumors
- Poor bladder function
- Carcinoma in situ
- Unable to obtain visible complete TURBT
- [Unable to tolerate chemotherapy]
- [Prior high dose radiation therapy]

- Side note: bladder mapping recommended and fiducials are helpful!
Radiation

- Logistics
- Consultation
- CT simulation
- RT planning
- RT delivery
Radiation: Target delineation

- Whole vs partial bladder
- Lymph node coverage vs bladder only
- CT urogram or MRI (particularly prior to TURBT)
- Fiducials

*Lee Target Planning 2015*
IMRT vs 3DCRT

Lee Target Planning 2015, Sondergaard 2009
Radiation: Regimen

- Prescription dose
  - ~64Gy over ~6.5 weeks vs 55Gy over ~4 weeks (i.e. hypofractionated)

- BC2001 (CRUK / 01 / 004)
  - Phase III: RT +/- synchronous 5FU and MMC
    - Quasi 2x2, also randomized to:
      - Whole bladder vs reduced bladder RT
      - 64Gy/32 vs 55Gy/20
  - 360 pts with muscle-invasive bladder ca
  - Huddart IJROBP 2013
    - 2y RTOG grade 3/4 toxicity lower than expected, at 13%
    - No SS reduction in late side effects between whole vs reduced bladder RT
    - Noninferiority of locoregional control could not be concluded formally
Radiation: Regimen

- ASTRO 2019 abstract
  - BC2001 and BCON Meta-analysis
    - 64Gy/32 vs 55Gy/20
  - 782 pts; mean age 72, 80% stage T1/2
  - Median f/u 120 mo
  - 29% lower risk of invasive ILRR with 55Gy
    - Benefit still present with RT alone
  - No OS difference
  - Similar toxicity profile
    - Difference in absolute risk of grade ≥3 late bladder or rectum symptom of -3.82%
  - Concluded 55Gy noninferior in terms of ILRC, OS and late toxicity and superior for ILRC but not OS
Quality of life after bladder pres.

- Urodynamics study and patient reported QOL at MassGen
  - Zietman J Urol 2003; Mak IJROBP 2016
  - 75% survivors had normal functioning bladders
    - 6% had difficulty with urinary flow
    - 15% with urinary urgency
    - 19% with incontinence
  - 22% with bowel symptoms
  - 36% normal erections, another 18% weaker but sufficient for intercourse
  - Patient reported QOL similar to slightly better general QOL, bowel symptoms, sexual function for bladder preservation vs cystectomy
Quality of life after bladder pres.

- Pooled RTOG studies (89-03, 95-06, 97-06, 99-06)
  - Efstathiou JCO 2009
  - 157 pts who survived at least 2 years with intact bladder
  - Late grade 3 GU toxicity <6%
  - Late grade 3 GI toxicity <2%

- Typically occurred within 2 years of therapy, lasted median ~7 months and rarely persisted
- No late grade 4 toxicities, treatment related deaths or cystectomy due to toxicity
Combined modality: Role of immunotherapy?
## Metastatic bladder cancer

In 2016, first new FDA approved drug

<table>
<thead>
<tr>
<th>First-line systemic therapy for locally advanced or metastatic disease (Stage IV)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cisplatin eligible</strong></td>
</tr>
<tr>
<td>Preferred regimens</td>
</tr>
<tr>
<td>• Gemcitabine and cisplatin(^a) (category 1)</td>
</tr>
<tr>
<td>• DDMVAC with growth factor support (category 1)(^b,8)</td>
</tr>
<tr>
<td><strong>Cisplatin ineligible</strong></td>
</tr>
<tr>
<td>Preferred regimens</td>
</tr>
<tr>
<td>• Gemcitabine and carboplatin(^11)</td>
</tr>
<tr>
<td>• Atezolizumab(^12) (only for patients whose tumors express PD-L1(^a) or who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression)</td>
</tr>
<tr>
<td>• Pembrolizumab(^13) (only for patients whose tumors express PD-L1(^b) or who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression)</td>
</tr>
<tr>
<td>Other recommended regimens</td>
</tr>
<tr>
<td>• Gemcitabine(^14)</td>
</tr>
<tr>
<td>• Gemcitabine and paclitaxel(^15)</td>
</tr>
<tr>
<td>Useful under certain circumstances</td>
</tr>
<tr>
<td>• Ifosfamide, doxorubicin, and gemcitabine(^16) (for patients with good kidney function and good PS)</td>
</tr>
</tbody>
</table>

\(^a\) Atezolizumab: PD-L1–stained tumor-infiltrating immune cells covering ≥5% of the tumor area.

\(^b\) Pembrolizumab: Combined Positive Score (CPS) ≥10.
Immune checkpoint inhibitors

- Mechanism of action
  - Programmed death-1 (PD-1) expressed on surface of immune cells
  - Programmed death ligand-1 (PD-L1) expressed on cancer cells
    - When joined, form a biochemical “shield” protecting tumor cells from immune system mediated destruction
  - → PDL1 inhibitors block this interaction
Immune checkpoint inhibitors

• 5 available for the treatment of bladder cancer
  • atezolizumab (Tencentriq®)
  • pembrolizumab (Keytruda®)
  • nivolumab (Opdivo®)
  • avelumab (Bavencio®)
  • durvalumab (Imfinzi®)

• If unable to receive chemotherapy: atezolizumab or pembrolizumab
• If progression/recurrence after chemotherapy: any
ASCO 2019: Vofatamab in Combination with Pembrolizumab in WT Metastatic Urothelial Carcinoma: FIERCE-22

ASCO 2019: Targeted Therapeutics and Patient Selection in Advanced Urothelial Carcinoma

ASCO 2019: Classification and Management of Infrequent Genitourinary Malignancies

ASCO 2019: Clinical Outcomes According to PD-L1 Status and Age in the Prospective International SAUL Study of Atezolizumab for Locally Advanced or Metastatic Urothelial Carcinoma or Non-UC of the Urinary Tract

ASCO 2019: Atezolizumab in Upper Tract Urothelial Carcinoma vs Urothelial Carcinoma of the Bladder and Association with Comprehensive Genomic Profiling/Cell-free DNA Results

ASCO 2019: Randomized, Double-Blind, Placebo-Controlled Phase III Trial Comparing Gemcitabine and Cisplatin with Bevacizumab or Placebo in Patients with Metastatic Urothelial Carcinoma — CALGB 90601 (Alliance)

ASCO 2019: Phase II Study of Nivolumab and Ipilimumab for Advanced Bladder Cancer of Variant Histologies

ASCO 2019: FIERCE-22: Clinical Activity of Vofatamab - FGFR3 Selective Inhibitor in Combination with Pembrolizumab in WT Metastatic Urothelial Carcinoma - Medical Oncologist Perspective

ASCO 2019: A Pilot Safety Study of Gemcitabine and Cisplatin with Atezolizumab as First-Line Therapy in Patients with Metastatic Urothelial Cancer

ASCO 2019: A Phase II Study of Investigational Antibody-drug Conjugate RC48 in Human Epidermal Growth Factor Receptor 2 Positive Patients with Locally Advanced or Metastatic Urothelial Carcinoma

ASCO 2019: Novel Treatment Strategies in Metastatic Urothelial Carcinoma

ASCO 2019: Defects in DNA Repair Genes and Long-Term Survival in Cisplatin-Based Neoadjuvant Chemotherapy for Muscle-Invasive Bladder Cancer

ASCO 2019: Pembrolizumab Versus Placebo After First-Line Chemotherapy In Patients With Metastatic Urothelial Carcinoma
Immunotherapy + chemotherapy

- ESMO 2019 annual meeting
  - IMvigor130 trial presented by Dr Grande
    - 1213 pts from 35 countries with untreated locally advanced or metastatic urothelial cancer
    - Randomization:
      - A) Atzeolizumab + platinum based chemo
      - B) Atezolizumab alone
      - C) Platinum based chemo plus placebo
    - Median f/u 11.8mo
  - Results
    - 18% decreased risk of progression for combo arm (8.2 vs 6.3mo)
    - Trend towards improved OS (16 vs 13.4mo arms A and C) not SS
    - 13% complete response rate in combo arm (vs 6% and 7%)
  - Early results – longer f/u needed
Chemoradiotherapy with or without Atezolizumab in Treating Patients with Localized Muscle Invasive Bladder Cancer

STATUS: ACTIVE

Description

This phase III trial studies how well chemotherapy and radiation therapy work with or without atezolizumab in treating patients with localized muscle invasive bladder cancer. Radiation therapy uses high energy rays to kill tumor cells and shrink tumors. Drugs used in chemotherapy, such as gemcitabine, cisplatin, fluorouracil and mitomycin-C, work in different ways to stop the growth of cancer cells, either by killing the cells, by stopping them from dividing, or by stopping them from spreading. Giving chemotherapy with radiation therapy may kill more tumor cells. Immunotherapy with monoclonal antibodies, such as atezolizumab, may help the body’s immune system attack the cancer, and may interfere with the ability of tumor cells to grow and spread. Giving atezolizumab with radiation therapy and chemotherapy may work better in treating patients with localized muscle invasive bladder cancer compared to radiation therapy and chemotherapy without atezolizumab.

Eligibility Criteria
Ongoing studies – new drugs

- Enfortumab Vedotin
  - Antibody-drug conjugate (ADC)
  - Anti-Nectin-4 monoclonal antibody attached to synthetic cell-killing agent, monomethyl auristatin E (MMAE)

- EV-201 study: First novel therapeutic with substantial response for patients who progress after platinum chemo and PDL1 inhibitor
  - 44% response rate
  - 7.6mo median duration response
Conclusions

- Treatment options for bladder cancer
  - Neoadjuvant chemotherapy → radical cystectomy and LND
    - Better OS with chemotherapy
    - Cisplatin-based regimen preferred
  - Bladder conserving concurrent chemoradiation
    - Non-cystectomy candidates or carefully selected patients
    - Prospective / retrospective studies have shown good outcomes in carefully selected patients
      - RT vs CRT: better LR control with CRT
    - Note contraindications:
      - Tumor >4-5cm, hydronephrosis / ureter, multifocal tumors, poor bladder function, CIS, unable to obtain visible complete TURBT, unable to tolerate chemo/RT
      - Impact on bladder function but rates of late toxicities are low

- Systemic advances:
  - Immunotherapy
Thanks for listening!