Muscle-Invasive Bladder Cancer

Risk Stratification, Multidisciplinary Treatment, Metastatic Disease, & Diversion Derangements

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Acknowledgments

SLIDES

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Disclosures

- Advisory Boards: Pfizer, Merck, Protara
- Consulting: Aura, UroGen
- Clinical Trials: UroGen, Pfizer, CG Oncology, Fidia, EnGene, Merck
- Study Chair for EA8212

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Muscle-Invasive Bladder Cancer Outline

- Epidemiology
- Staging
- Treatment
  - Radical cystectomy
  - Lymphadenectomy
  - Chemotherapy
  - Bladder Preservation
- Urinary Reconstruction
- Metastatic Bladder Cancer

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EPIDEMIOLOGY

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Natural History

- 25% of newly diagnosed bladder cancer invades muscle
- Among patients presenting with MIBC:
  - 70% present with localized disease
  - 30% have regional spread
  - 5% have distant metastasis

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Siegel RL, Cancer statistics 2020

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Patterns of Bladder Cancer Dissemination Can Occur Independently

Hematogenous Spread

- 33% of patients who die with bladder cancer do not have nodal metastasis
- Sites
  - Liver (38%)
  - Lung (36%)
  - Bone

Lymphatic Spread

- Correlated with
  - Extent of local tumor (T stage)
  - Adverse pathology
    - Lymphovascular invasion
- Sites
  - Perivesical (16%)
  - Obturator (74%)
  - External iliac (65%)
  - Presacral, internal iliac (25%)

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STAGING

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Clinical Staging

- Bi-manual examination at TURBT (must obtain muscle)
- Labs
  - CBC, BMP, LFTs, Alk phos
- Imaging
  - Chest (CT or chest x-ray)
  - Abdomen/pelvis with IV contrast (CT or MRI)
- Optional
  - Bone scan IF elevated alkaline phosphatase or bone pain
  - PET IF determining mets before cystectomy (LN accuracy 80%)

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TNM Staging Invasive Cancer (AJCC 8th Edition 2017)

- T1 – invades lamina propria invasion
- T2 – invades muscularis propria (2a = inner half, 2b = outer half)
- T3 – invades perivesical tissue (3a = microscopic, 3b = macroscopic)
- T4 – invades prostatic stroma, SV, uterus, vagina (4a), pelvic, abd wall(4b)

UC arising from prostatic urethra alone and not spread from bladder ≠ T4a and does not alter primary tumor stage (considered **pT2**)

Presence of **Hydronephrosis or Palpable Mass** on Post-TUR Bi-Manual Exam indicates **extravesical disease** (≥T3)

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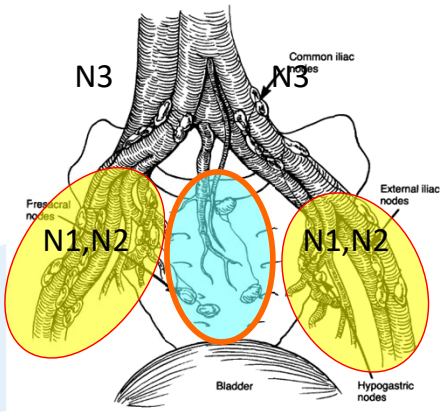
TNM Staging Invasive Cancer (AJCC 8th Edition 2017)

- N1 – single node in true pelvis
- N2 – multiple nodes in true pelvis
- N3 – common iliac nodes

**True pelvis includes external and internal iliac, obturator and pre-sacral nodes*

**>12 nodes for adequate staging*



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Additional Poor Prognostic Factors

- Variant histology
- Lymphovascular invasion
- Number of lymph nodes involved
- Extracapsular nodal extension
- Size of largest tumor deposit in lymph nodes

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Staging

Stage	T	N	M
I	T1	N0	M0
II	T2a T2b	N0 N0	M0 M0
IIIA	T3a T3b T4a T1-T4a	N0 N0 N0 N1	M0 M0 M0 M0
IIIB	T1-T4a	N2, N3	M0
IVA	T4b Any T	Any N Any N	M0 M1a
IVB	Any T	Any N	M1b

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Staging

Stage	T	N	M
I	T1	N0	
II			
IIIA			M0
IIIB	T1-T4a	N2, N3	M0
IVA	T4b Any T	Any N Any N	M0 M1a
IVB	Any T	Any N	M1b

Stage **I**: Invasive into **Lamina Propria**
Stage **II**: Invasive into **Muscularis Propria**
Stage **III**: **Nodal** involvement
Stage **IV**: **Metastasis** or Invades Body Wall

SURGERY

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Radical Cystectomy (Male)

- Removal of:
  - Bladder and perivesical fat
  - Prostate, seminal vesicle, and prostatic urethra (AUA Guideline Statement #11)
- Concurrent Urethrectomy rarely performed
  - If positive urethral margin demonstrated on final path (rare) – can perform a delayed urethrectomy
- AUA MIBC Guideline Statement #12: “Clinicians should discuss and consider sexual function preserving procedures in patient with organ-confined disease and absence of bladder neck, urethra, and prostate (male) involvement.”

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Radical Cystectomy (Female)

- Removal of bladder +/- gynecologic organs
- Can consider Anterior Exenteration on case by case basis (Guideline Statement #11):
  - Uterus, cervix, tubes, ovaries, anterior vagina
- Vaginal and nerve-sparing techniques may be considered for localized disease which can preserve sexual function
- EUA and pelvic MRI can aide in determining safety of organ preservation

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Ureteral Margins

- Distal ureteral margin can be sent for frozen section to ensure absence of frank carcinoma
- Presence of CIS does not mandate negative frozen sections
  - Remove what is reasonable to ensure adequate length with negative margin and preserve kidney
  - Positive margin does not correlate with outcomes

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Surgical Approach

- Open vs. Laparoscopic (Robotic)
  - Robotic non-inferior to open for 2-year PFS
- Potential advantages of robotic:
  - Decreased blood loss (and transfusion rates)
  - Increased magnification
- Potential disadvantages of robotic:
  - Increased operative time (and cost, in some studies)
  - Higher rates of postop carcinomatosis in earlier series

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Surgical Approach?

- Several randomized trials now report on RARC vs. ORC
  - MSKCC trial: single institution
  - RAZOR trial: multicenter, *non-inferiority* trial
  - iROC (Catto et al, JAMA 2022)
  - IRCCS, Rome RCT (Mastroianni J Urol 2022)

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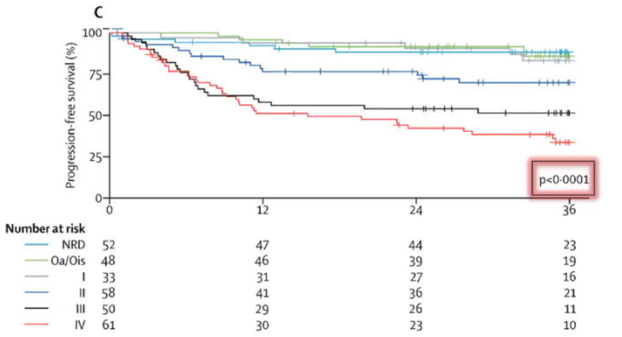
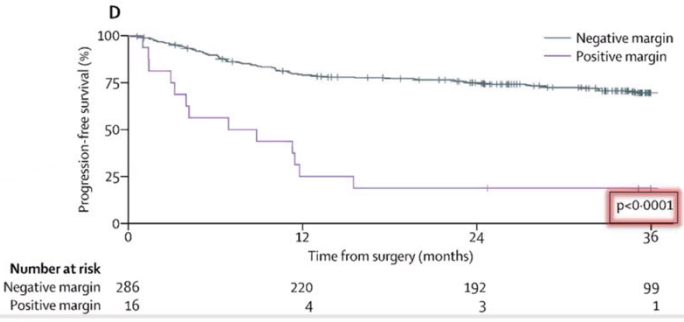
RAZOR trial

Results – 2-year PFS by pT



Kaplan-Meier estimate of progression-free survival by pathological T stage

Results – 2-year PFS by Surgical Margin



Kaplan-Meier estimate of progression-free survival by Surgical margin

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Venkatramani, J Urol 2020

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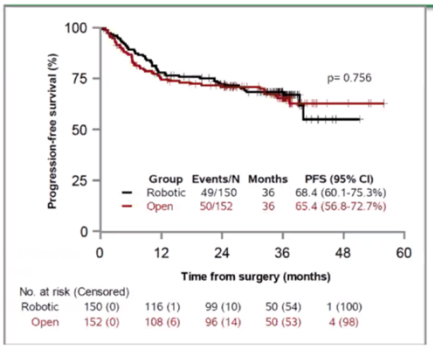
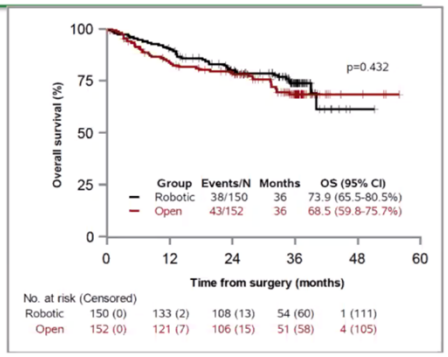
RAZOR trial

Results – 3-year PFS and OS *(J Urol, 2020)*



3-year Progression Free Survival



3-year Overall Survival

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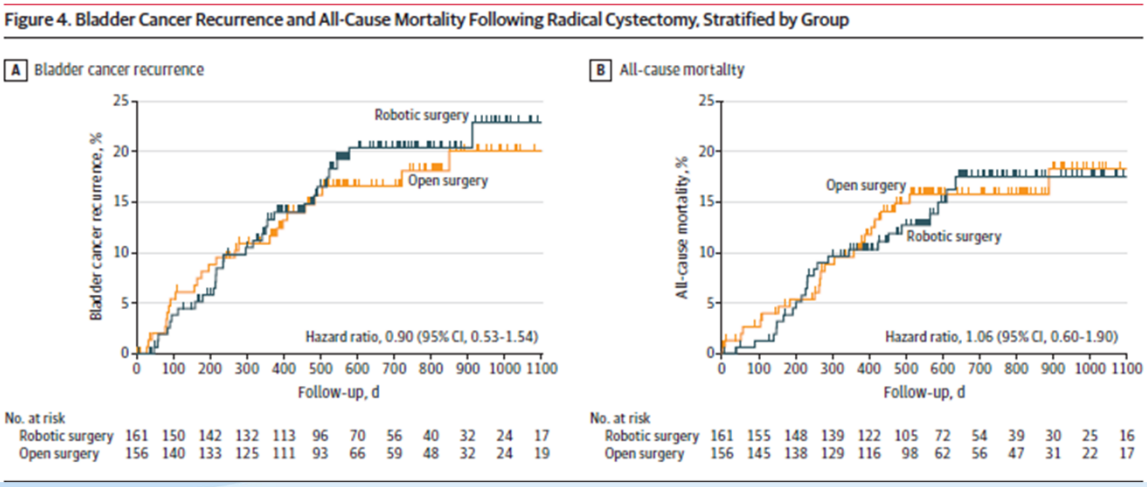
Venkatramani et al, J Urol 2020

iROC trial

- Median Followup 18 months



Catto. JAMA 2022

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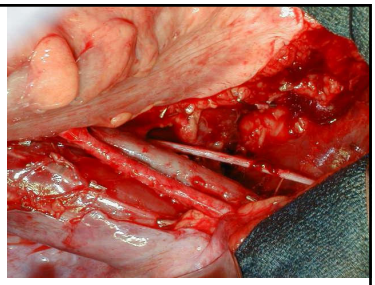
Lymphadenectomy



- Diagnostic and potentially therapeutic
- Standard template is now supported over extended
- Phase III RCT (n=401) in MIBC limited vs. extended LND
  - OS 52 vs. 71 months
  - RFS 65% vs. 59% (non-significant difference)
- SWOG S1011
  - No difference in disease free or overall survival between standard and extended
  - Extended associated with more Grade 3-5 AEs (54% vs 44%) and 90 Day Mortality (7% vs 2%)

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Gschwend Eur Urol 2019
Lerner NEJM 2024

Boundaries of a Lymphadenectomy

Margin	Landmarks
Distal	Node of Cloquet
Proximal	Extent: • **Standard**: bifurcation of common iliac • **Extended**: bifurcation of inferior abdominal aorta • **Superextended**: aorta at origin of IMA
Lateral	Genitofemoral nerve
Inferior	Internal iliac lymph nodes, pelvic floor
Posterior	Sacrum

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Cystectomy Complications

Table 4: Complications following radical cystectomy using standardized reporting methodology

Gastrointestinal *	Ileus, small bowel obstruction, emesis, peptic ulcer, anastomotic bowel leak, enterocutaneous fistula, ascites, GI bleed, diarrhea, c. difficile
Infection *	Fever of unknown origin, pelvic/retroperitoneal abscess, urinary tract infection, incisional, peritonitis, diverticulitis, cholecystitis, sepsis
Wound	Dehiscence, wound seroma, wound infect
Cardiac	Myocardial infarct ina
Genitourinary	Acute re ry retention, bladder r
Pulmonary	Atelectas
Bleeding	Anemia re p hemorrhage, flank hematoma, wound hematoma, scrotal hematoma,
Thromboembolic	Deep venou ary embolus, superficial phlebitis, subclavian vein thrombosis
Neurologic	Nerve palsy, paralysis, loss of consciousness, agitation, delirium, CVA, vertigo
Miscellaneous	Psych illness, tendonitis, dermatitis, acidosis, thrombocytopenia without bleeding, foot ulcer, lymphocele, decubitus ulcer
Surgical	Incisional hernia, vascular injury, retained drain, rectal injury, obturator nerve injury, enterotomy

* most common complication

See reference Shabsigh2009

64% experience at least 1 perioperative complication (13% are high grade)

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Reducing Perioperative Morbidity

- Preoperative evaluation/optimization of cardiac and pulmonary function
- ERAS (enhanced recovery after surgery)
  - Minimize perioperative GI complications
  - Reduce hospital stay
  - Reduce readmissions

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ERAS Pathways

Perioperative

- No bowel prep
- Minimize Intraoperative Fluids
- Carbohydrate Loading
- Alvimopan (mu-receptor antagonist)–prevent ileus ***
- Minimize blood loss & bowel manipulation

Postoperative

- No NGT
- Advance diet early
- Chewing Gum
- Alvimopam
- Non-opioid pain control
- Routine anti-emetics
- Venous thromboprophylaxis***
- Early mobilization

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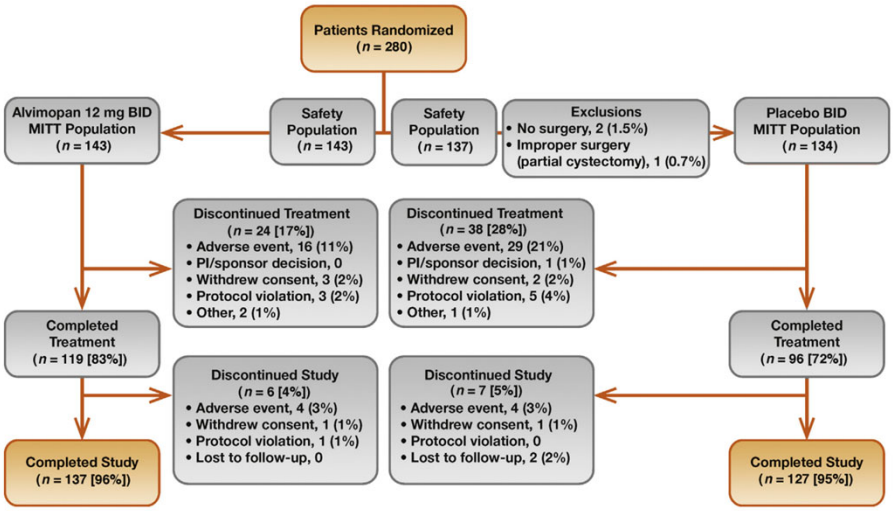
(*** Statement in AUA MIBC Guideline)

RCT Supporting Alvimopam Usage



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Lee, *European urology* 2014

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RCT Supporting Alvimopam Usage

End point	Alvimopan 12 mg (n = 143)	Placebo (n = 134)	Difference (95% CI)	p value
Time to GI-2 recovery				
HR (95% CI)	1.8 (1.4, 2.3)	–	–	<0.0001*
KM, d, median (IQR)	4.9 (4.0, 5.8)	6.1 (4.7, 8.9)	−1.2	–
KM, d, mean (SE)	5.5 (0.18)	6.8 (0.23)	−1.3 (−1.9 to −0.7)	–
Time to DOW				
HR (95% CI)	1.7 (1.3, 2.2)	–	–	0.0002*
KM, d median (IQR)	6.7 (5.7, 7.7)	7.5 (5.7, NC)	−0.8	–
KM, d mean (SE)	6.9 (0.2)	7.8 (0.2)	−0.9 (−1.5 to −0.4)	–
Postoperative LOS, d				
Median (range)	7.0 (4.0, 22.0)	8.0 (4.0, 77.0)	−1.0	
Mean (SD)	7.44 (3.05)	10.07 (8.23)	−2.63	0.0051†
Prolonged LOS (>7 d), %	32.9	51.5	−18.6%	<0.010‡
POI-related morbidity, %	8.4	29.1	−20.7%	<0.001‡

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CHEMOTHERAPY

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Rationale for Neoadjuvant Chemotherapy

- Rationale
  - Treat micro-metastatic disease up front
  - Downstage “unresectable” to “resectable”
  - Only for those w/o contraindications to chemotherapy
- RCT neoadjuvant MVAC w/ cystectomy (Grossman)
  - Median survival 77 vs. 46 months
  - Absolute improvement in OS of 5-7%
  - Absolute improvement in CSS of 9%

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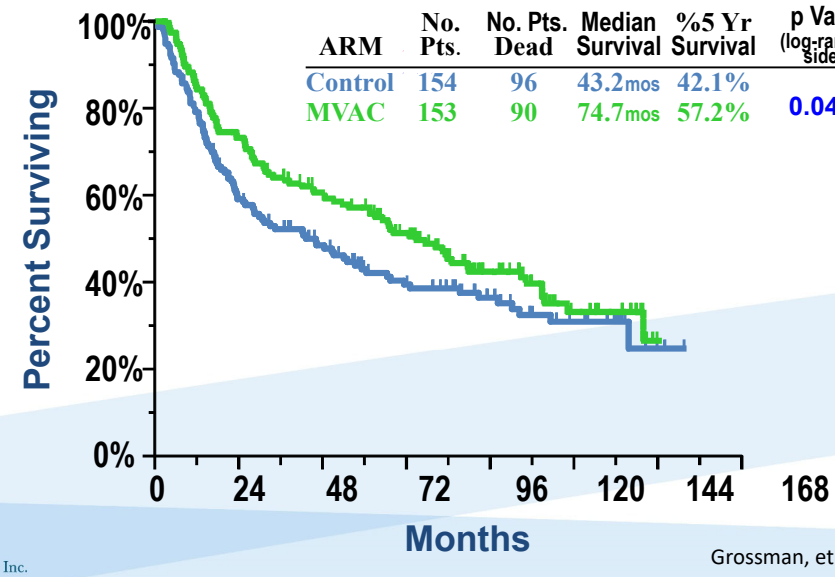
SWOG 8710: Overall Survival by Treatment Arm



ARM	No. Pts.	No. Pts. Dead	Median Survival	%5 Yr Survival	p Value (log-rank, 1-sided)
Control	154	96	43.2mos	42.1%	
MVAC	153	90	74.7mos	57.2%	0.044

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Grossman, et al NEJM 349:859, 2003

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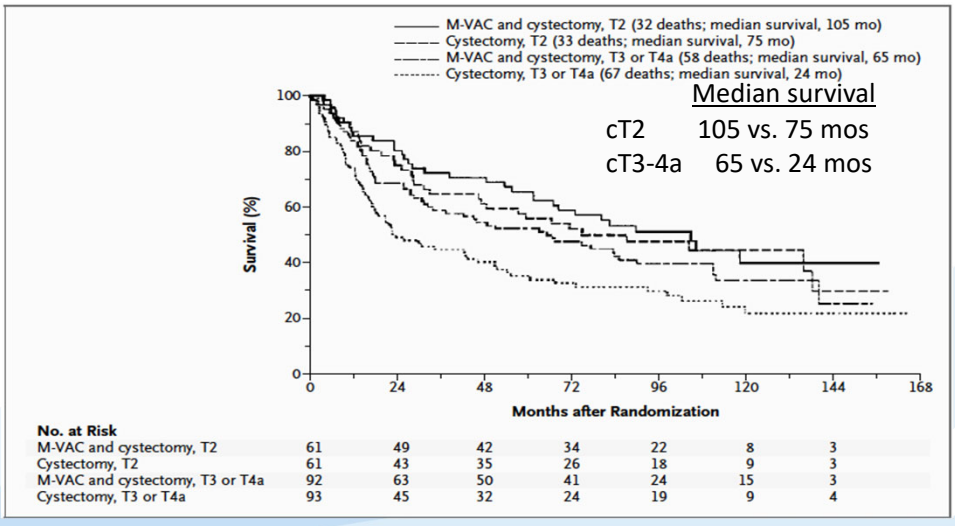
SWOG 8710 Neoadjuvant MVAC- Benefit cT2 vs. cT3-T4a

Pts with cT2 also benefit from neoadjuvant chemotherapy



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Grossman, et al NEJM 349:859, 2003

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Neoadjuvant Chemo Regimens

Classic MVAC	Dose Dense MVAC	GC
28-day cycle	**14-day cycle**	**21-day cycle**
	(3-6 cycles)	(4 cycles)
Methotrexate	Methotrexate	Gemcitabine
Vinblastine	Vinblastine	Cisplatin
Doxorubicin	Doxorubicin	
Cisplatin	Cisplatin	
	Pegylated G-CSF	

Preferred

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Chemotherapy Agents

Chemo Agent	Mechanism	Side Effects
Methotrexate	anti-folate; inhibits dihydrofolate reductase	Stomatitis, **increased reabsorption across bowel**
Vinblastine	vinca alkaloid; inhibits microtubule assembly	Stomatitis, **neurotoxicity**
Doxorubicin	anthracycline antibiotic inhibit DNA and RNA synthesis and topoisomerase II	Stomatitis, alopecia (common), red colored urine, **cardiomyopathy** (dose dependent)
Cisplatin	cross-links DNA and forms adducts	**Nephrotoxicity**, **ototoxicity**, emesis, **neuropathy**, myelosuppression
Gemcitabine	nucleoside analogue, inhibits thymidylate synthetase and blocks DNA synthesis	Vomiting, **myelosuppression** (**thrombocytopenia** > leukopenia)

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Slide 35

0 Accelerated GC?

Rena Kates, 2024-03-22T14:52:03.687

Contemporary Neoadjuvant Regimens

- Gemcitabine/Cisplatin
  - Phase III (MVAC vs GC) – similar OS
  - GC better tolerated
- Dose Dense MVAC
  - Better tolerated
  - Fewer treatment delays
  - Shorter treatment course
  - Borderline significant RRR of progression/death

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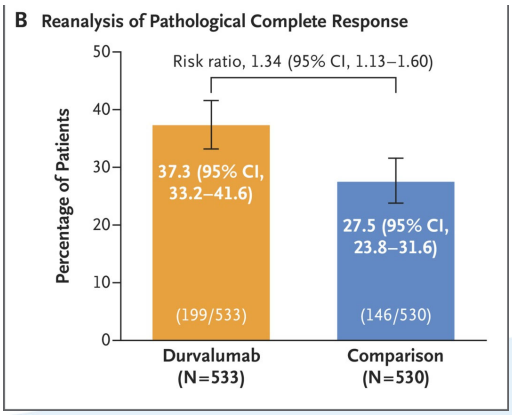
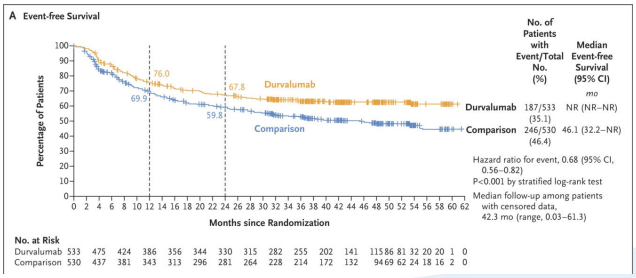
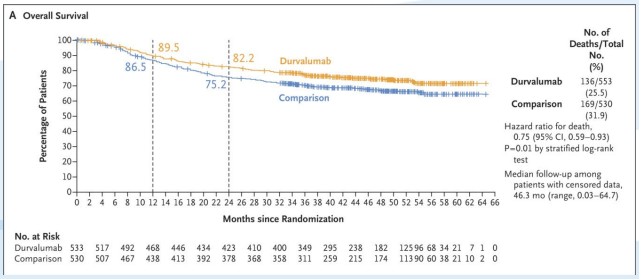
Niagara Protocol- Cisplatin/Gemcitabine/Durvalumab







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Powles T et al. N Engl J Med2024;391:1773-1786

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Guidelines? AUA, EAU, ASCO

- Neoadjuvant chemotherapy with cisplatin based multi-agent regimen standard of care
  - AUA: Strong Recommendation; Evidence Level: Grade B
- M-VAC/CMV only regimens tested in Phase III trials

**Common use of GC based on patients with metastatic disease and has not been evaluated in Phase III neoadjuvant trials

Dash et al. Cancer 2006;107:506-13

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Eligibility for Cisplatin-based therapy

- Renal function
  Based on GFR / Creatinine clearance
  - GFR > 60 : standard dosing
  - GFR 50-60: consider split-dosing, extra hydration
  - GFR <50: rarely eligible
- Hearing Loss
  - Cis toxicity manifests as sensorineural hearing loss with tinnitus
- Peripheral neuropathy
- Functional status: ECOG 0-1

An estimated 40-50% of patients not eligible for cisplatin

Dash et al. Cancer 2006;107:506-13

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Adjuvant Systemic Therapy

- Treatment after cystectomy for patient with no evidence of disease but at **high risk for recurrence**

- Criteria
  - Cystectomy path:
    - Extravesical disease (pT3-T4) or Residual pT2 after NAC
    - Nodal disease (N+)
- Options
  - Nivolumab (12 months)
    - Level I evidence UCB, UTUC
  - Gemcitabine + Cisplatin
    - Level I evidence UTUC

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Bajorin, NEJM 2021; Birtle Lancet 2020 (update 2021 GU-ASCO)

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Post-Cystectomy Surveillance

- **Schedule of tests per AUA Guidelines (Statement #30)**
  - Clinicians should obtain chest imaging and cross sectional imaging of the abdomen and pelvis with CT or MRI at 6-12 month intervals for 2-3 years and then may continue annually. (Expert Opinion)
- **Labs (CBC, BMP, LFTs, B12) (Statement #31)**
  - Following therapy for muscle-invasive bladder cancer, patients should undergo laboratory assessment at three to six month intervals for two to three years and then annually thereafter. (Expert Opinion)

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Urethral Recurrence Risk

- Involvement of prostatic urethra associated with higher risk of urethral recurrence in men
- Involvement of bladder neck/anterior vaginal wall strongest predictor in women

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Urethral Recurrence

- Bloody urethral discharge mandates urethroscopy (with urethral wash and biopsy)
- Non-Invasive
  - TURBT
- Invasive
  - Urethrectomy with urethral meatus
  - Conversion to ileal conduit easiest using afferent limb
  - Can convert to continent catheterizable stoma

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BLADDER PRESERVATION

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Bladder Preservation

- Partial Cystectomy
- Tri-Modal Therapy: Chemoradiation with maximal TUR

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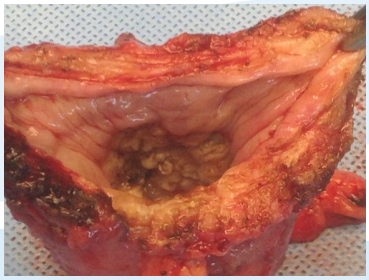
Partial Cystectomy

- Indications
  - Tumor within a bladder diverticulum
  - Solitary tumor at the dome
  - Urachal adenocarcinoma
- Risk factors for recurrence
  - CIS
  - Multifocal lesions
  - Positive surgical margins
  - Lymph node involvement



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Partial Cystectomy

- Treatment
  - **Urothelial**: Consider NAC + lymph node dissection
  - **Urachal**: Resect posterior rectus sheath, urachus, and bladder dome en bloc (closed technique)
- Cystoscopic surveillance required
- Outcomes
  - Overall 5-year survival 69%
  - Overall bladder preservation 74%

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Tri-Modal Therapy (TMT)

- Ideal candidates
  - Organ-confined disease
  - No hydronephrosis
  - Size <3cm
  - No (or minimal) CIS
  - Urothelial histology (no variant)
- Survival similar to cystectomy
  - Salvage cystectomy rate 20%

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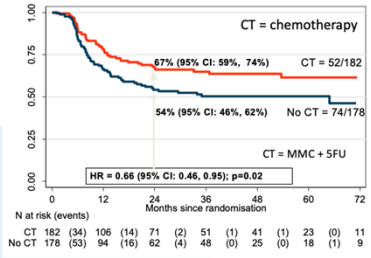
Chemoradiation

- Maximal TUR improves response
- Radiosensitizing chemo improves response
  - 5-fluorouracil and mitomycin
  - Single agent cisplatin
  - Single agent gemcitabine (CIS ineligible)
- External beam radiation
  - Doses typically 60-66 Gy
  - Two doses chemo given on weeks 1 and 4



James, et al NEJM 366:1477, 2012

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Post TMT Surveillance

- Surveillance regimens follow similar schedule as high risk NMIBC
  - Cystoscopy every 3 months x 2 years, 6 months x 2 years, annually thereafter
  - Bladder recurrence → TURBT first (some recur as NMIBC and can be treated as such)
  - Chest imaging, CT abdomen/pelvis every 3-6 months

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URINARY RECONSTRUCTION

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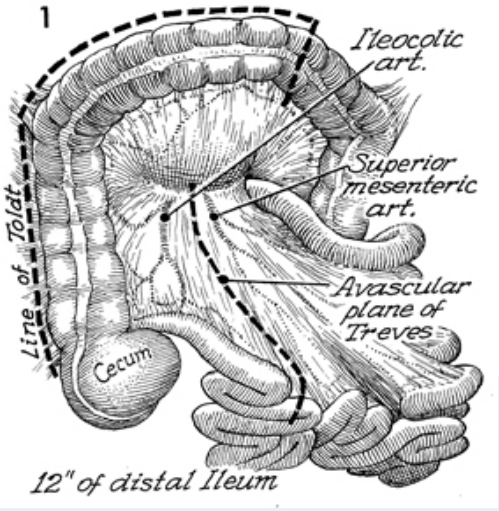
Bowel Segment Anatomy



- Small bowel reservoir based on SMA – divide mesentery between ileocolic and terminal branches of SMA
- Collateral blood supply from Marginal artery of Drummond
- Right colon reservoir based on ileocolic/right colic arteries. Divide bowel proximal to middle colic artery

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Wheeless, Roenneberg Atlas of Pelvic Surgery on line ed

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Advantages of Small Bowel

- Lower pressures than colon
- Reliably reaches the urethra
- Facilitates taking ureters high (e.g. XRT, CIS)
- Low incidence ureteral stricture (4%)
- Urine is frequently sterile
- Very low incidence of late complications

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Ileal Conduit

- Most commonly performed diversion
- Advantages
  - Simple to perform
  - Easy to manage with high satisfaction rate
- Disadvantages
  - Fear of odor/leakage
  - External appliance
  - Restricted social and sexual activities (in some cases)

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Ileal Conduit: Outcomes

- Majority of studies suggest no difference in QOL compared to continent diversions
- 54% develop a complication within 15 years
  - ~20-27% renal function decline
  - ~15-24% stomal complications
  - ~10-20% bowel issues
  - ~16-25% UTI

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Madersbacher t al, J Urol 2003
Shimko t al, J Urol 2011

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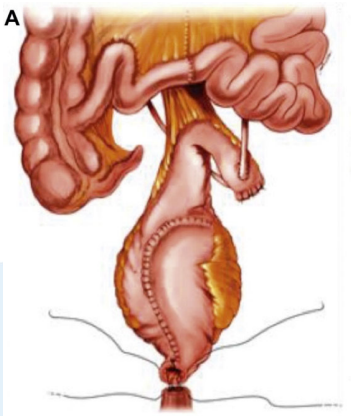
Orthotopic Diversions

- Most commonly performed is Studer pouch
  - Afferent limb draining into a low-pressure ileal reservoir
- Most important intraoperative consideration is urethral margin (frozen section mandatory-Guideline Statement #14)



Studer Pouch

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Orthotopic Contraindications

- Positive intraoperative urethral margin
- Pubic bone involvement
- Neurologic disease that impairs dexterity
- Severe stress urinary incontinence
- Urethral stricture disease
- **Chronic renal failure**
  - **GFR < 40 or Cr > 1.8**
- Hepatic insufficiency
- Chronic inflammatory bowel disease
- Malignant bowel disease

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Orthotopic Diversion Selection

- Ensure patient has ability to catheterize *if necessary* (more common in women)
- Do not routinely exclude:
  - Elderly patients
  - Prior irradiation – distal ileum preferred
  - T3b, T4a or N+ patients

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Orthotopic Diversion Outcomes

- Incontinence
  - Daytime 10-15%
  - Nighttime 20-50%
  - Related to **loss of afferent input from detrusor to CNS**
  - No increase in urethral resistance during filling
  - Nerve-sparing associated with optimal urinary continence
- Urinary retention
  - Women: 50-60%
  - Men: 10% (if de novo, consider recurrence or bladder neck contracture)
- Complications
  - UTI 2-5%
  - Bowel complications 3-12%
  - Urolithiasis 1%

Hautmann, J Urol 2010
Studer, J Urol 2006
Bartsch Worl J Urol 2014
Thurairaja, R, et al BJUI 2008

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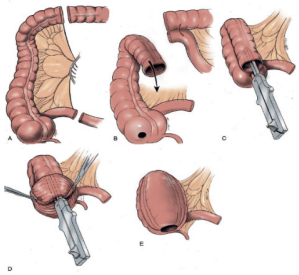
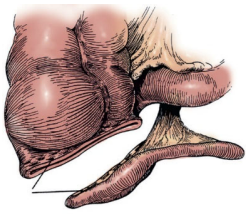
Continent Cutaneous Diversion

Stapled Indiana Pouch



Appendix/Mitrofanoff



- Most include R colon as reservoir
- Continence mechanisms
  - Tapered ileal segment (Indiana Pouch)
  - Appendix using ileocecal valve (Mitrofanoff)

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Continent Cutaneous Selection

- Life expectancy > 1 year
- Strong self-image to be “bag free”
- Manual dexterity
- Adequate renal function
- Normal bowel function
- Pre-operative colonoscopy

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Continent Cutaneous Stoma

- Stoma site
  - Right lower quadrant typical
  - Umbilicus
    - Concealable
    - Very easy to perform
    - Great with obese patients

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Continent Cutaneous Outcomes

- Continence
  - Daytime 96%
  - Nocturnal 74%
- Difficult catheterization (5%)
- Stomal stenosis (<5%)

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Complications of Urinary Diversions

EARLY

- Stricture or breakdown of ureteroileal anastomosis
- Bowel obstruction
- Ureter or bowel leak
- Infection
- Pouch-vaginal fistula

LATE

- Ureteral strictures
- Nephrolithiasis
- Stomal complications
- Metabolic complications
- Infection
- Urethral recurrence

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Urine Leak

- Prevention through stents
  - Some recommend stents 3-4 weeks
- Risk is 2-10%
- Can lead to fibrosis and stricture if untreated
- Percutaneous drainage or nephrostomy tube as initial step in most cases

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Bowel Leak

- Occurs in <3%
- Can lead to abdominal abscess, sepsis
- Conservative management if no signs/symptoms
  - Empiric antibiotics
  - Drainage of fluid/abscess
  - Nutritional support (TPN)
- Most cases require **abdominal exploration and repair**

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Pouch-Vaginal Fistula

- Unique to **orthotopic** neobladder
- Occurs in 5-10% of patients
- **Persistent urine leakage despite catheter** placement
- More common in **radiated patients**
- Diagnosis with cystoscopy and plain film or **CT cystogram**
- Treatment is **surgical**; rarely heal spontaneously

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Ureteral Strictures

- **Loopogram** to identify reflux (r/o obstruction)
- Anastomotic strictures are usually due to ischemia of distal ureter
  - **Early** (<1 yr) and **short** (<2cm) respond to **dilation and stenting**
  - **Late** (>1 yr) and **long** (>=2cm) usually require **re-implantation**
- Urine cytology to **rule out urothelial cancer recurrence**
- Strictures **not** at anastomosis
  - Rule out **second primary** urothelial cancer

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Urolithiasis

- Prevalence depends on diversion (12%)
- **Renal** calculi
  - **Metabolic acidosis**
  - **Chronic infection** (struvite stones)
- **Reservoir** calculi
  - Foreign body/**staples**
  - **Obstruction** (pouch retention = crampy pain)
- Treatment depends entirely on location/cause
  - ESWL
  - Endoscopic removal
  - Laparoscopic or open removal (e.g. Indiana pouch)

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Conduit Ischemia

- Normal post op venous congestion
- Should “pink up” over first few days post op
- If turns black – lubricated test tube + penlight or endoscopy to determine extent
- May require urgent surgical revision or debridement

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Stomal Stenosis

- Diagnosis: gloved finger into os
- Symptoms:
  - UTIs
  - Flank pain
  - Decreased UOP
  - Projectile urine
- Treatment:
  - Stomal dilation with finger, medical dilator
  - Local excision and re-mature stoma

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Diarrhea

- Pathophysiology
  - Decreased absorptive capacity
  - Loss of ileocecal valve
  - Fat malabsorption
  - Bile salt irritation of colon
- Treatment
  - Psyllium (adds bulk to stool)
  - Atropine and diphenoxylate
  - Loperamide
  - Cholestyramine – absorbs bile salts

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Acidosis

- Hyperchloremic hypokalemic acidosis most common with ileum/colon
- Renal impairment decreases ability to compensate
- Occurs from excess ammonia introduced by urinary tract
  - Ammonium takes place of Na in Na-H exchangers
  - Causes exchange of bicarb for chloride
  - Net gain of Cl and H+ and loss of bicarb
- Treatment
  - Alkalinization with sodium bicarb
  - If can't use sodium, then chlorpromazine or nicotinic acid can be tried
- Common in 70% acute; 33% chronic

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B12 Deficiency

- Incidence requiring replacement 5%
- Risk factors:
  - Loss of ileocecal valve and distal terminal ileum
  - Use of ~50 cm ileum
  - Radiation therapy
- Diagnosis: Monitor annually
  - Usually takes 3-4 years to deplete but can occur earlier
- Symptoms
  - Neurologic (lethargy, fatigue, memory loss, headaches, paresthesias)
- Treatment
  - IM B12 supplementation (oral doesn't absorb well)

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Metabolic Complications

		BLOOD						
SEGMENT	SYNDROME	Na^+	K^+	Cl^-	pH	ASSOCIATED ABNORMALITIES	SYMPTOMS	TREATMENT
Stomach	Severe metabolic alkalosis	—	↓	↓	↑	Elevated aldosterone	Lethargy, muscle weakness, respiratory insufficiency, seizures, ventricular arrhythmia	H_2 blocker, proton pump inhibitor; if life-threatening, arginine hydrochloride infusion and/or removal of segment
Jejunum	Hyperkalemic, hypochloremic metabolic acidosis	↓	↑	↓	↓	Elevated renin and angiotensin	Lethargy, nausea, vomiting, dehydration, muscle weakness	IV hydration, sodium bicarbonate, thiazide; if life-threatening, removal of segment
Ileum/colon	Hyperchloremic metabolic acidosis	—	↓	↑	↓	Total-body potassium depletion, hypocalcemia	Fatigue, anorexia, lethargy, weakness	Potassium citrate, sodium citrate, citric acid, sodium bicarbonate, chlorpromazine, nicotinic acid

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Wintner A and Dahl DM Use of Intestinal Segments in Urinary Diversion, in Campbell-Walsh urology, 12th edition

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Metabolic Consequences

- Stomach →Less permeable to urinary solutes and net excretion of Cl- and H+
  - **Hypochloremic Hypokalemic Metabolic Alkalosis →** can be severe in those with Dehydration & Azotemia → Inc Aldostreone & impaired HCO3- excretion
    - Symptoms: Lethargy, Seizure, Resp Failure, Arrhythmias
    - Treatment--> Stable Patients H2 Blockers, PPI as 2nd choice
      - Life-threatening scenario -Argenine Hydrocholoride infusion to restore acid-base balance
  - Hematuria Dysuria Syndrome- up to 24%
    - Bladder spasms, pain, hematuria, skin excoriation- Tx w/ H2 Blockers

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1. Weese JR and Radadia KD Bladder Reconstruction AUA Core Curriculum
2. Wintner A and Dahl DM Use of Intestinal Segments in Urinary Diversion, in Campbell-Walsh urology, 12th edition

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Metabolic Consequences

- Jejunum→ practically speaking Not Used!! TESTABLE!
  - Loss of significant Jejunum→ malabsorption of Fat, Calcium and Folic Acid
  - **Hyponatremia, Hypochloremia, Hyperkalemic Metabolic Acidosis**
    - Esp w/ Prox Jejunum and w/ TPN
    - Lethargy, N/V, Dehydration and weakness
  - Treatment→0.9% NaCL Fluids + Bicarb
    - Long Term- Oral NaCl, Thiazides have also been used for Hyperkalemia
    - If persistent issues- Remove Jejunal segment used

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Metabolic Consequences

- Ileum/Colon-
  - Hyperchloremic Hypokalemic Metabolic Acidosis- Incidence ~25%
    - Symptoms→ Anorexia, Weight-Loss, Polydipsia, Lethargy
    - Result of Ammonium Chloride absorption
    - Treatment- Alkalizing agent or Block Cl transport
      - Oral Sodium Bicarb→ Start 650mg BID/TID and titrate causes bloating/gas
      - Oral Sodium Citrate and Citric Acid Solution (Bicitra); Oral Potassium Citrate/Sodium citrate
      - If Persistent hyperchloremic acidosis and want to reduce Na load- can use chlorpromazine (25mg TID) or nicotinic acid (Niacin-Vit B3) (400mg TID)→ cAMP inhibition and reduce Cl transport
        - » Avoid Nicotinic Acid if Peptic Ulcer or Liver Dysfunction

1. Weese JR and Radadia KD Bladder Reconstruction AUA Core Curriculum
2. Wintner A and Dahl DM Use of Intestinal Segments in Urinary Diversion, in Campbell-Walsh urology, 12th edition

Metabolic Consequences

- Altered Sensorium
  - Magnesium Deficiency→ Renal Mg wasting or nutritional depletion
  - Hyperammonemia –in patients with altered liver fxn and/or cirrhosis
    - Can result in Ammoniagenic Coma:
      - Treatment→ Drain diversion with catheter-reduce urine contact time with bowel
      - Oral Neomycin –reduces ammonia load from GI
      - Arginine Glutamate (50g in 1L D5W) for severe cases
      - Lactulose
- Abnormal Drug Absorption- Phenytoin, Methotrexate

1. Weese JR and Radadia KD Bladder Reconstruction AUA Core Curriculum
2. Wintner A and Dahl DM Use of Intestinal Segments in Urinary Diversion, in Campbell-Walsh urology, 12th edition

Metabolic Consequences

- Vit B12 Malabsorption with Loss of Ileal Length
  - Megaloblastic Anemia and Neurologic Abnormality
  - May take more than 3-5 years from surgery to manifest
  - Can replace with VitB12 injection or with Nasal Spray
    - often just treat in patient > 5years with diversion
- Malabsorption of Bile Salts with loss of Ileal Length
  - Cause mucosal irritation and diarrhea, lipids not absorbed well
  - Cholestyramine- sequesters bile acids- reduces diarrhea
    - Long-term use can result in Vit D, A, E, K deficiency

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Metabolic & Functional Issues

- Loss of Ileocecal Valve→
  - Reflux of Colonic Bacteria into Ileum→ small intestinal overgrowth
    - Interferes with Fatty Acid Reabsorption and Bile Salt Interaction and bile salt deficiency
      - Bile Salt and Fatty Acids in colon →diarrhea
      - Inability to absorb fat- can result in Fat Soluble Vitamin deficiency, Vit A, D, E and K
  - Decreased GI transit time with loss of IC valve, also decreased absorption b/c faster transit
  - Avoid resection in Myelomeningocele- may exacerbate diarrhea, fast transit and alter bowel function[3,4]

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1. Weese JR and Radadia KD Bladder Reconstruction AUA Core Curriculum
2. Wintner A and Dahl DM Use of Intestinal Segments in Urinary Diversion, in Campbell-Walsh urology, 12th edition
3. King LR et al, Experiences with bladder reconstruction in children J urol 1987
4. Estrada CR and Bauer SB. Neuromuscular dysfunction of the lower urinary tract in children in Campbell-Walsh Urology, 12th edition

METASTATIC BLADDER CANCER

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Bladder Cancer Metastases

- Less than 5% of patients initially present with metastatic bladder cancer beyond the pelvic lymph nodes.
- 50% of patients with muscle invasive bladder cancer will progress to metastatic disease despite curative local therapy.
- The median duration of survival following the diagnosis of metastatic bladder cancer is 2 years.
- Broad changes to Treatment Paradigm with multiple new FDA approved therapies in recent years

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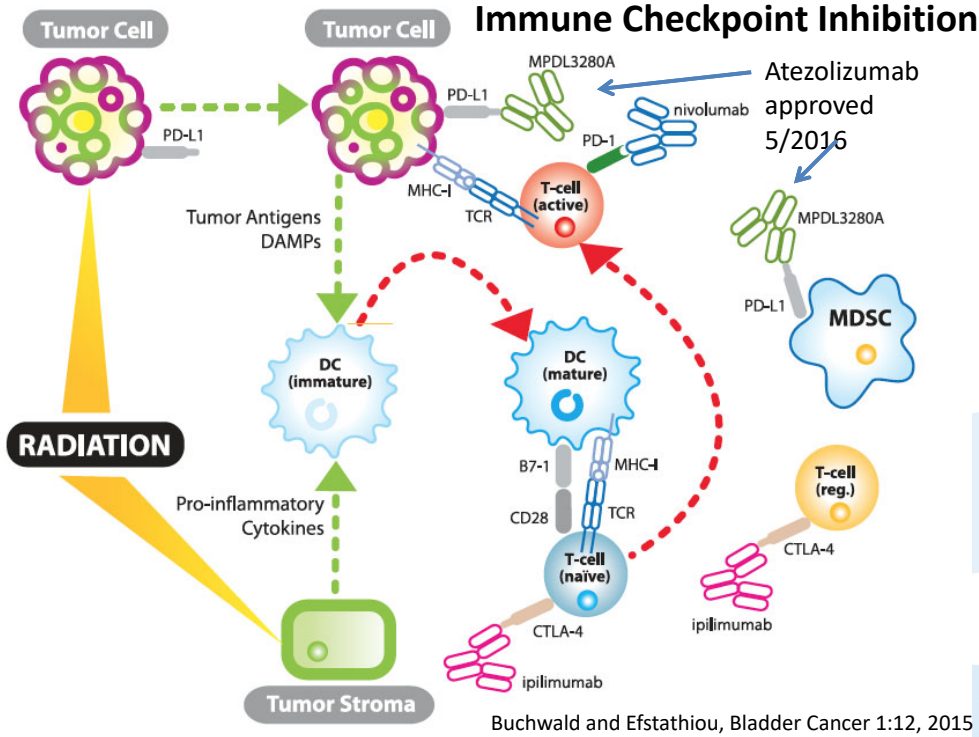

Buchwald and Efstathiou, Bladder Cancer 1:12, 2015

Immune Checkpoint Inhibitors

- PD-1 is expressed on activated T cells
- PD-L1 is its binding partner, expressed on tumor cells
- Antibodies that target PD-1 and PD-L1 generate anti-tumor immunity by inhibiting negative T cell signaling

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Predictors of Checkpoint Response

- High tumoral immune cell expression of PD-L1
- High tumor mutational burden
- Luminal subtype (vs. basal)

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Immunotherapy Side Effects

Common (but mild)

- Fatigue
- Pruritis
- Nausea
- Diarrhea
- Asthenia
- Anemia

Uncommon (but serious)

- Endocrinopathies
- Pneumonitis
- Cardiomyopathy
- Hepatitis
- Colitis
- Myositis
- Severe skin reactions

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Immunotherapy Side Effects

Common (but mild)

- Fatigue
- Pruritis
- Nausea
- Diarrhea
- Asthenia
- Anemia

Uncommon (but serious)

- Endocrinopathies
- [illegible]s
- [illegible]athy
- [illegible]patitis
- Colitis
- Myositis
- Severe skin reactions

Hold (or stop) Treatment
Treat with **Steroids**

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1st Line Systemic Chemotherapy Regimens: Cisplatin-Eligible

- Enfortumab Vedotin + Pembrolizumab (EV+pembro): FDA approved 12/2023
- Cis-Gem-Nivo: FDA approved 3/2024
- ddMVAC OR GC Followed by Avelumab maintenance (if no progression)

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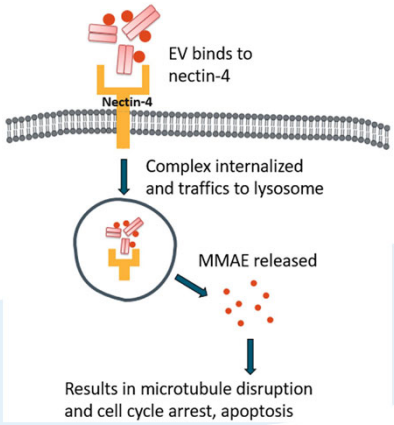
Enfortumab Vedotin

- Nectin-4 directed antibody drug conjugate
- Initially FDA approved as a monotherapy in the 3rd line for metastatic bladder cancer after cisplatin chemotherapy (if cis eligible) and PD-1/PD-L1 checkpoint inhibitor.
- Now approved (and used) in combination with pembrolizumab for patients with locally advanced or metastatic UC



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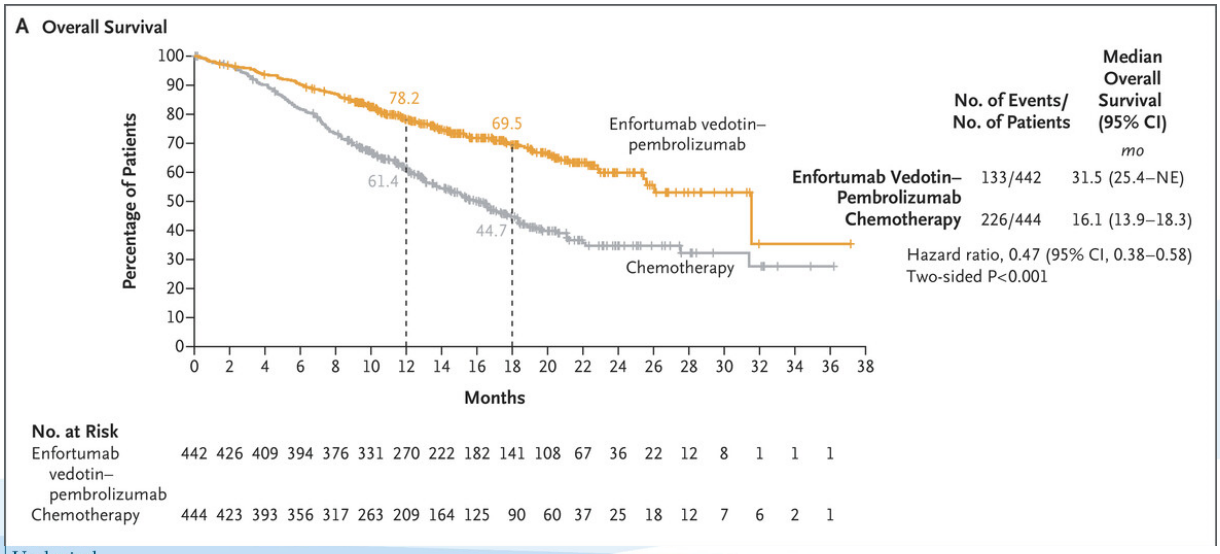
EV+ Pembro for Metastatic Bladder Cancer



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Powles, NEJM, 2024

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1st Line Systemic Chemotherapy Regimens: Cisplatin-Ineligible

Primary Option

- Pembrolizumab + Enfortumab (cisplatin-ineligible, approved 4/2023)

Secondary Options

- Gemcitabine + carboplatin followed by avelumab maintenance (if no progression)
- Atezolizumab (PD-L1+ or cisplatin-ineligible regardless of PD-L1 expression)
- Pembrolizumab (cisplatin-ineligible)

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Subsequent-Line Systemic Therapy

- Erdafitinib *(if FGFR3 or FGFR2 genetic alterations)*
- trastuzumab deruxtecan *(if Her2+)*

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Thank You
&
Good Luck!

Max.Kates@jhmi.edu

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ARS Question 1

- A 67 year old woman with muscle invasive bladder cancer undergoes 4 cycles of neoadjuvant chemotherapy followed by radical cystectomy. Final Pathology is pT0N1. The next best step is:
  1) Observation
  2) 2 more cycles of cisplatin based chemotherapy
  3) 1 year of nivolumab
  4) 1 year of enfortumab vedotin + pembrolizumab
  5) Radiation to pelvic floor and nodes

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ARS Question 2

- A 77 yo man has muscle invasive bladder cancer and desires bladder preservation. He has a PMH notable for COPD, CKD (GFR 35), and DM. The best approach for this patient would be:
  - A) Radiation Therapy Only
  - B) Radiation Therapy + cisplatin
  - C) Radiation Therapy + gemcitabine
  - D) Radiation Therapy + pembrolizumab
  - E) Radical Cystectomy with Adjuvant nivolumab

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ARS Question #3

- A 67 yo male with metastatic bladder cancer is in the middle of treatment when he complains of having urgent and frequent bowel movements. He is found to have lost 20 lbs despite a robust appetite. The best next lab value to check is:
- A) T4 and TSH
- B) B-12 and folate
- C) Calcium and AlkPhos
- D) C-Diff
- E) BMP

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