Current and Emerging Systemic Therapy Paradigms with Bladder Chemoradiation

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UNMC

Disclosures

Advisory Board: Exelixis, Inc., Lilly, Sanofi, Seagen Inc.

Consultant: ONVIV/Cancer Expert Now

INVESTIGATIONAL/OFF-LABEL USE OF DRUGS DISCLOSURE: Off-label drug discussion of Immunotherapy (Pembrolizumab/Nivolumab) in muscle-invasive bladder cancer

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Objectives

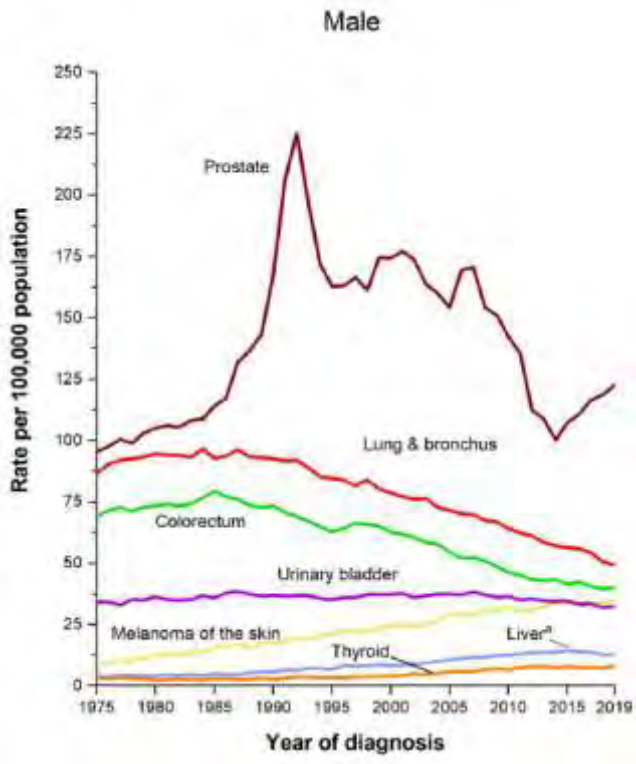
1. Compare current systemic therapies utilized for bladder trimodality therapy.

2. Explain emerging data on novel agents and immunotherapy in bladder sparing therapies.

3. Formulate a paradigm for optimal therapy selection for patients undergoing bladder sparing approaches to muscle-invasive bladder cancer.

Bladder Cancer- Epidemiology

82,290 cases for 2023



Estimated New Cases

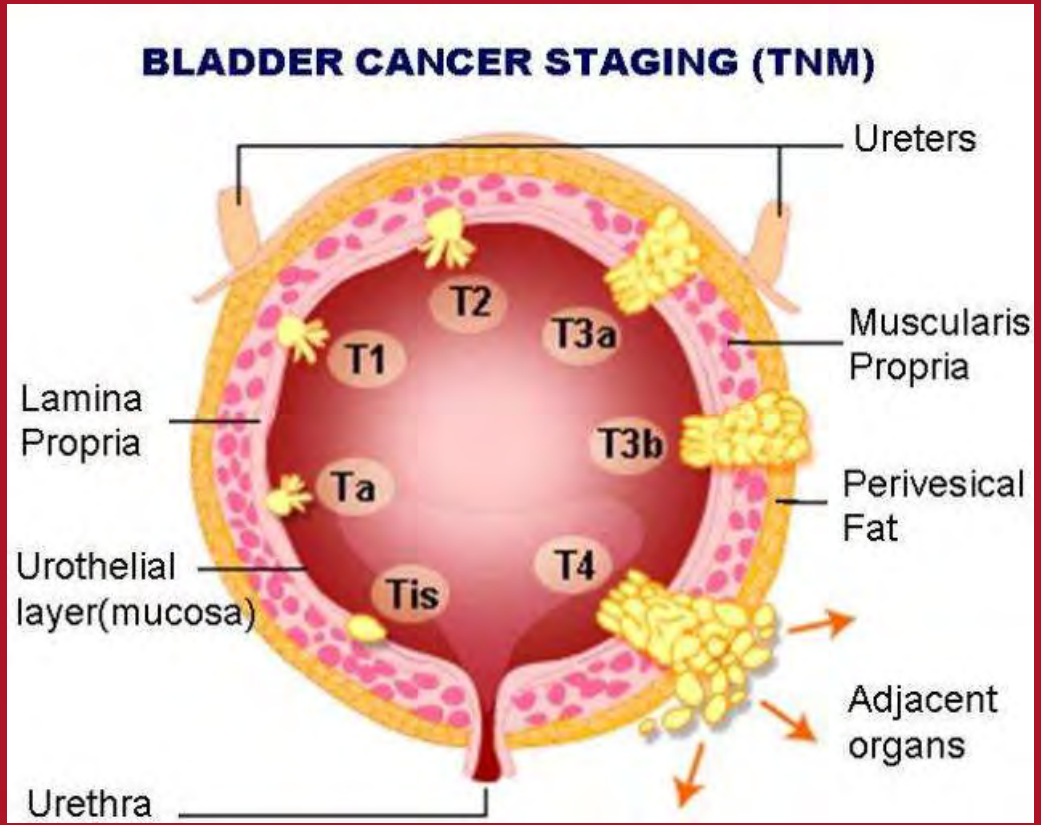
			Males	Females			
Prostate	288,300	29%			Breast	297,790	31%
Lung & bronchus	117,550	12%			Lung & bronchus	120,790	13%
Colon & rectum	81,860	8%			Colon & rectum	71,160	8%
Urinary bladder	62,420	6%			Uterine corpus	66,200	7%
Melanoma of the skin	58,120	6%			Melanoma of the skin	39,490	4%
Kidney & renal pelvis	52,360	5%			Non-Hodgkin lymphoma	35,670	4%
Non-Hodgkin lymphoma	44,880	4%			Thyroid	31,160	3%
Oral cavity & pharynx	39,290	4%			Pancreas	30,920	3%
Leukemia	35,670	4%			Kidney & renal pelvis	29,440	3%
Pancreas	33,130	3%			Leukemia	23,940	3%
All Sites	**1,010,310**	**100%**			**All Sites**	**948,000**	**100%**

Estimated Deaths

			Males	Females			
Lung & bronchus	67,160	21%			Lung & bronchus	59,910	21%
Prostate	34,700	11%			Breast	43,170	15%
Colon & rectum	28,470	9%			Colon & rectum	24,060	8%
Pancreas	26,620	8%			Pancreas	23,930	8%
Liver & intrahepatic bile duct	19,000	6%			Ovary	13,270	5%
Leukemia	13,900	4%			Uterine corpus	13,030	5%
Esophagus	12,920	4%			Liver & intrahepatic bile duct	10,380	4%
Urinary bladder	12,160	4%			Leukemia	9,810	3%
Non-Hodgkin lymphoma	11,780	4%			Non-Hodgkin lymphoma	8,400	3%
Brain & other nervous system	11,020	3%			Brain & other nervous system	7,970	3%
All Sites	**322,080**	**100%**			**All Sites**	**287,740**	**100%**

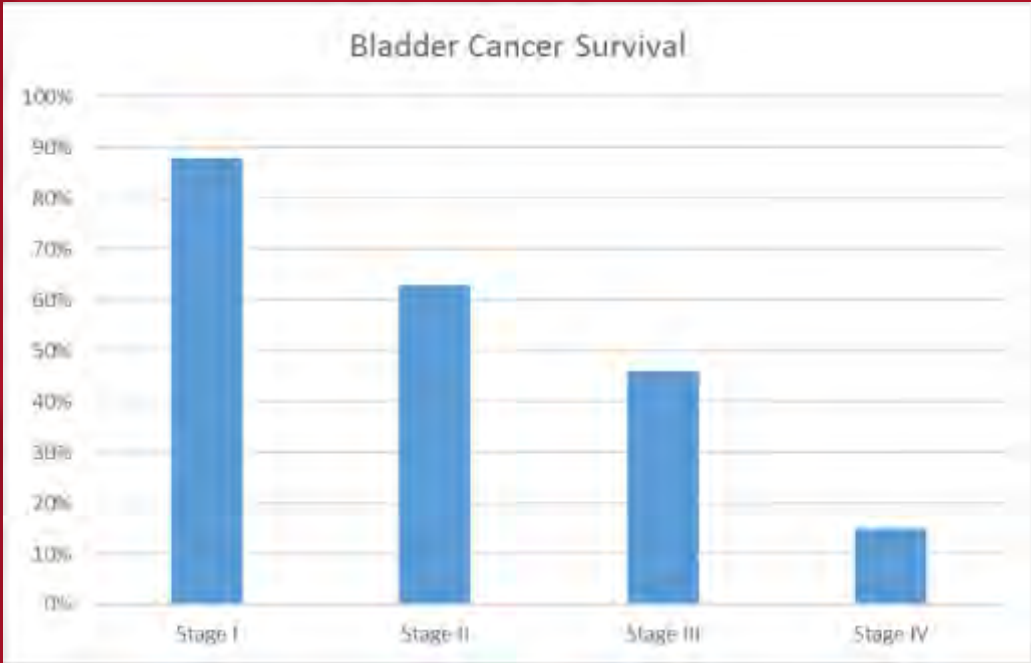
Bladder Cancer - Diagnosis

AJCC Staging



Bladder Cancer - Prognosis

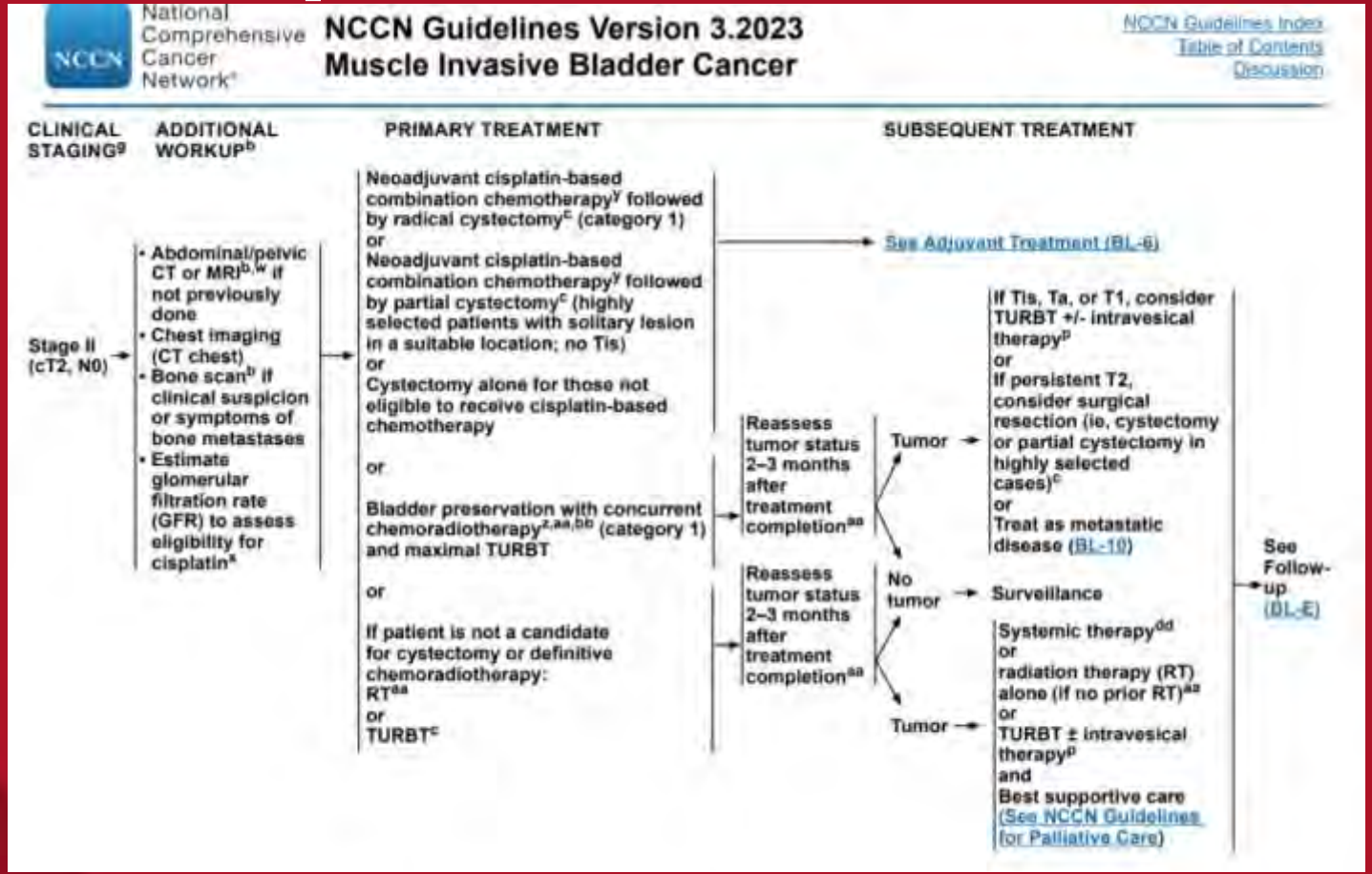
Risk at diagnosis



SEER Stage	5-year Relative Survival Rate
In situ alone	96%
Localized	70%
Regional	39%
Distant	8%
All SEER stages combined	77%

Cancer.org

Current Options for MIBC



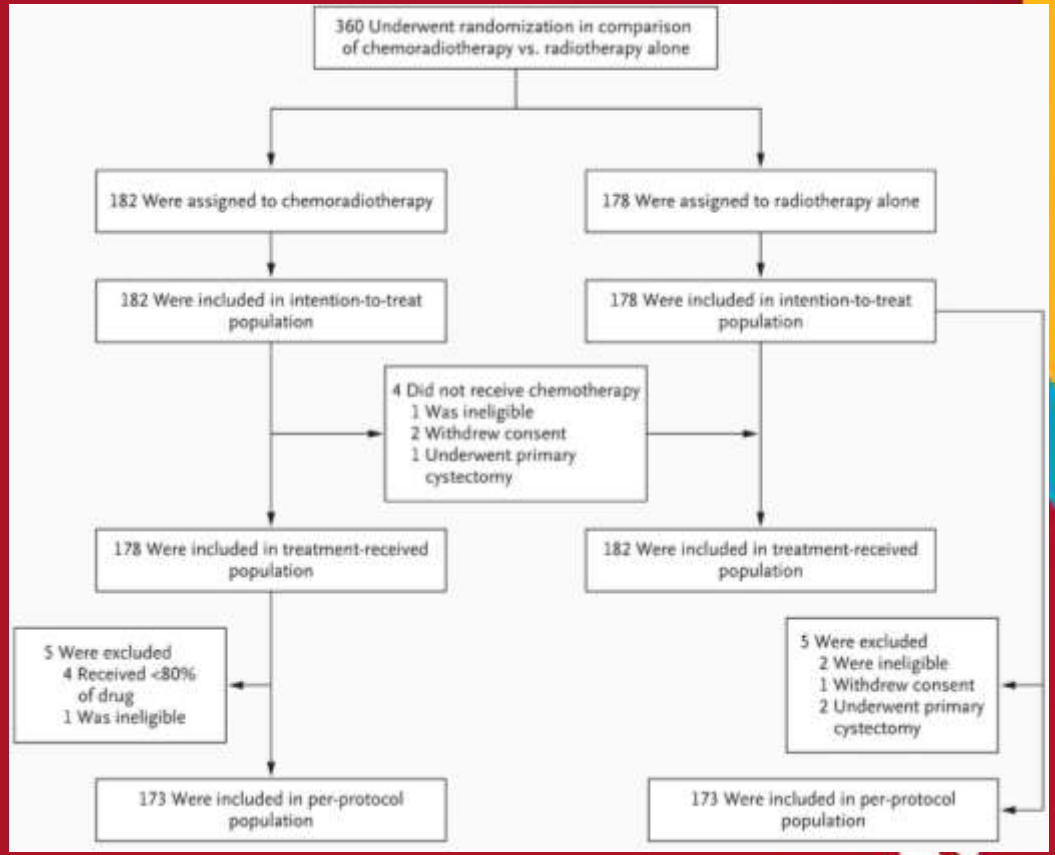
5FU + Mitomycin

BC2001 Phase 3 Clinical Trial

Eligibility (n=360):
- cT2 – cT4a cN0
- PS 0 – 2
- Neoadjuvant Chemo allowed

Randomization:
- Radiotherapy (whole bladder vs modified volume)
- Chemotherapy (yes or no)

Primary Endpoint:
- Locoregional control



N Engl J Med 2012;366:1477-1488.

5FU + Mitomycin

BC2001 Phase 3 Clinical Trial

Chemotherapy:

5FU: 500mg/m2/day D1-5 and D16-20 of radiotherapy

Mitomycin: 12mg/m2 D1 only

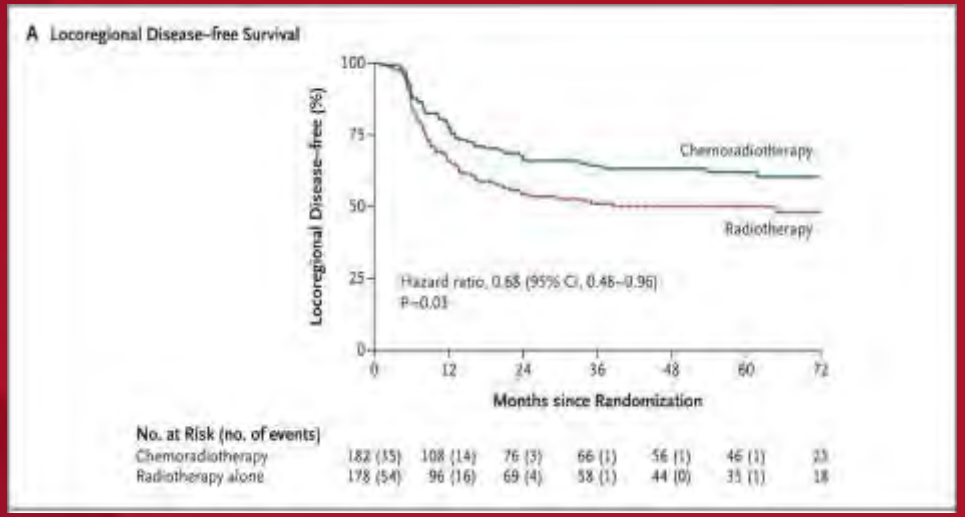
Table 1. Patient and Tumor Characteristics at Baseline.*

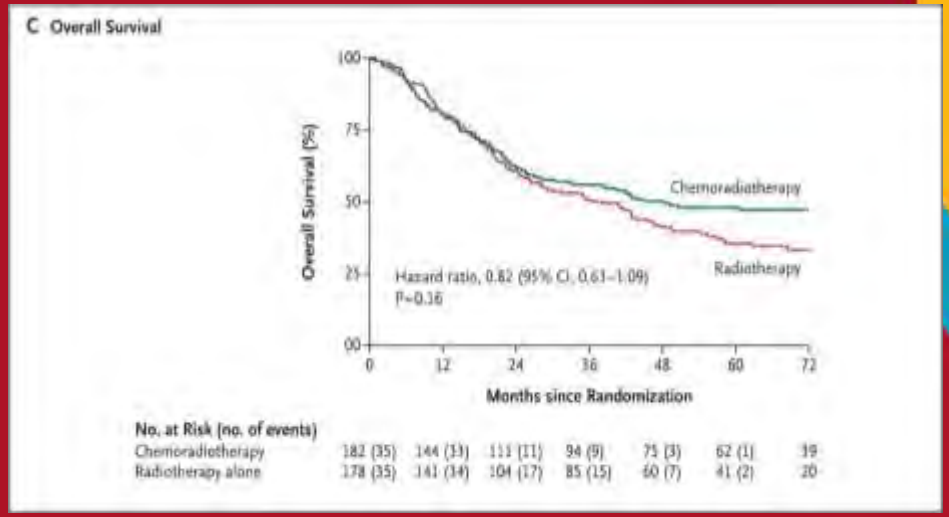
Characteristic	Chemoradiotherapy (N=182)	Radiotherapy (N=178)	All Patients (N=360)
Radiotherapy — no. (%)†			
Whole-bladder radiotherapy (randomized)	31 (17.0)	32 (18.0)	63 (17.5)
Modified-volume radiotherapy	33 (18.1)	25 (14.0)	58 (16.1)
Whole-bladder radiotherapy (not randomized)	118 (64.8)	121 (68.0)	239 (66.4)
Sex — no. (%)			
Male	149 (81.9)	140 (78.7)	289 (80.3)
Female	33 (18.1)	38 (21.3)	71 (19.7)
WHO performance status — no. (%)‡			
0	114 (62.6)	118 (66.3)	232 (64.4)
1	63 (34.6)	54 (30.3)	117 (32.5)
2	5 (2.7)	6 (3.4)	11 (3.1)
Age — yr			
Median	72.3	71.2	71.9
Interquartile range	65.1–76.6	63.7–75.9	64.1–76.2
Pathological stage of primary tumor — no. (%)			
1	0	1 (0.6)§	1 (0.3)
2	154 (84.6)	143 (80.3)	297 (82.5)
3a	10 (5.5)	15 (8.4)	25 (6.9)
3b	11 (6.0)	11 (6.2)	22 (6.1)
4a	7 (3.8)	7 (3.9)	14 (3.9)
Unknown	0	1 (0.6)	1 (0.3)
Transitional-cell carcinoma — no. (%)	177 (97.3)	175 (98.3)	352 (97.8)
Tumor resection — no. (%)¶			
Not resected	5 (2.7)	4 (2.2)	9 (2.5)
Biopsy	22 (12.1)	9 (5.1)	31 (8.6)
Complete resection	103 (56.6)	95 (53.4)	198 (55.0)
Incomplete resection	48 (26.4)	67 (37.6)	115 (31.9)
Unknown	4 (2.2)	3 (1.7)	7 (1.9)
Residual mass after resection — no. (%)¶			
Yes	48 (26.4)	52 (29.2)	100 (27.8)
No	122 (67.0)	117 (65.7)	239 (66.4)
Unknown	12 (6.6)	9 (5.1)	21 (5.8)
Neoadjuvant chemotherapy planned — no. (%)‖			
Yes	57 (31.3)	61 (34.3)	118 (32.8)
No	125 (68.7)	117 (65.7)	242 (67.2)
Planned radiotherapy schedule — no. (%)			
55 Gy in 20 fractions	71 (39.0)	71 (39.9)	142 (39.4)
64 Gy in 32 fractions	111 (61.0)	106 (59.6)	217 (60.3)
Unknown	0	1 (0.6)	1 (0.3)

N Engl J Med 2012;366:1477-1488.

5FU + Mitomycin

BC2001 Phase 3 Clinical Trial





N Engl J Med 2012;366:1477-1488.

5FU + Mitomycin

BC2001 Phase 3 Clinical Trial

Table 2. Worst Grade of Toxic Effects, According to Toxicity Criteria.*

Toxicity Criteria and Worst Grade	Chemoradiotherapy (N=178)	Radiotherapy (N=182)	Odds Ratio (99% CI)†	P Value‡
	no. (%)			
NCI CTCAE				
Any event				
Patients with data	178 (100.0)	182 (100.0)		
Grade 3–5	64 (36.0)	50 (27.5)	1.51 (0.83–2.74)	0.07
Genitourinary				
Patients with data	178 (100.0)	182 (100.0)		
Grade 3–5	38 (21.3)	39 (21.4)	1.00 (0.52–1.95)	0.99
Gastrointestinal				
Patients with data	178 (100.0)	182 (100.0)		
Grade 3–5	17 (9.6)	5 (2.7)	3.84 (0.97–15.19)	0.007

N Engl J Med 2012;366:1477-1488.

Cisplatin

RTOG 8802 Phase 2 Trial

Eligibility:

- cT2 – cT4a cN0 – cN2
- Neoadjuvant Chemo required

Cisplatin

- Q3 weekly (70mg/m2) for 2-3 doses

Primary Endpoint:

- Locoregional control

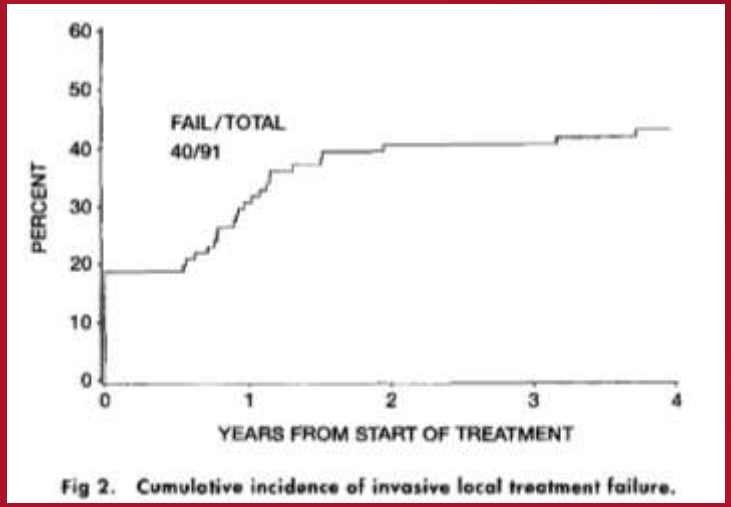


Fig 2. Cumulative incidence of invasive local treatment failure.

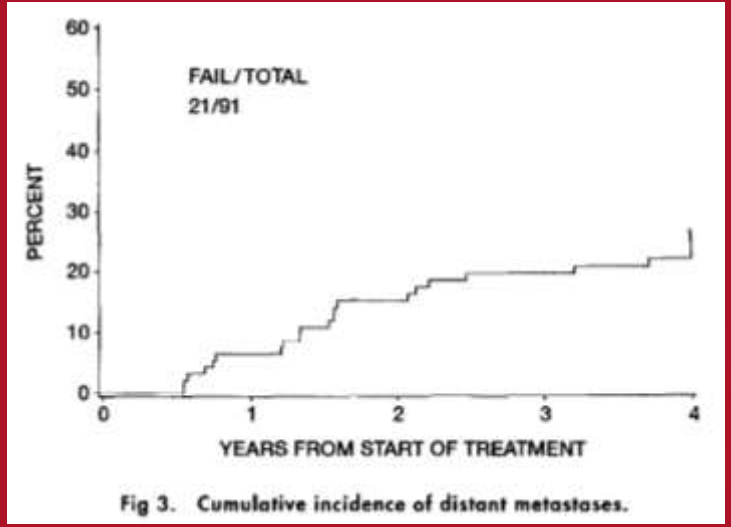


Fig 3. Cumulative incidence of distant metastases.

J Clin Oncol. 1996 Jan;14(1):119-26.

Cisplatin

TROG 97.01 & 99.06 Phase 2 Trials

Eligibility (n=113):

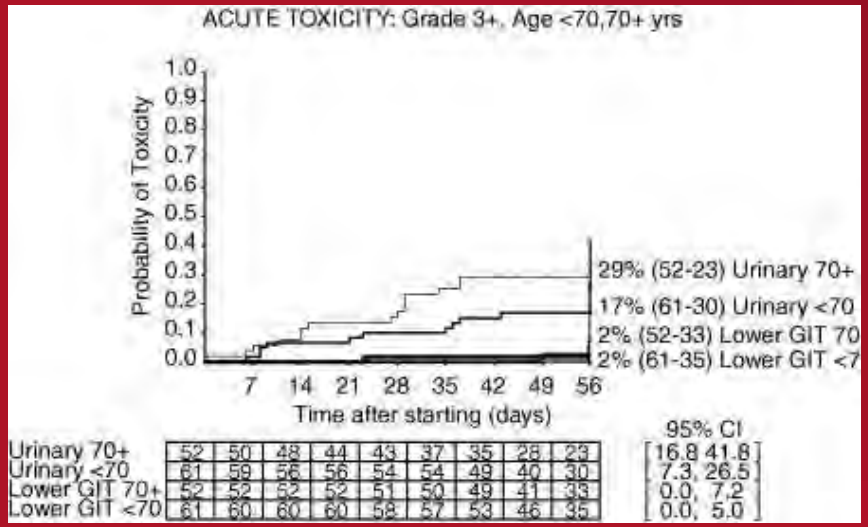
- cT2 – cT4a cN0
- CrCl > 60ml/min

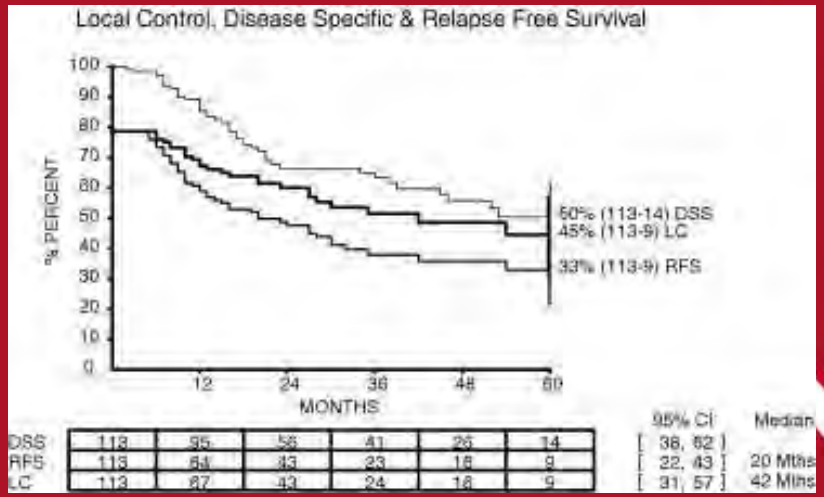
Cisplatin

- Weekly (35mg/m2)

Primary Endpoint:

- Acute Toxicity





Radiother Oncol. 2006 Oct;81(1):9-17.

Gemcitabine

NRG/RTOG 0712 Phase 2 Trial

Eligibility (n=33):

- cT2 – cT4a cN0
- ECOG PS 0-1
- Serum Cr < 1.5 mg/dL

Gemcitabine

- Twice Weekly (27mg/m2)

Primary Endpoint:

- Distant Metastasis Free Survival at 3 years

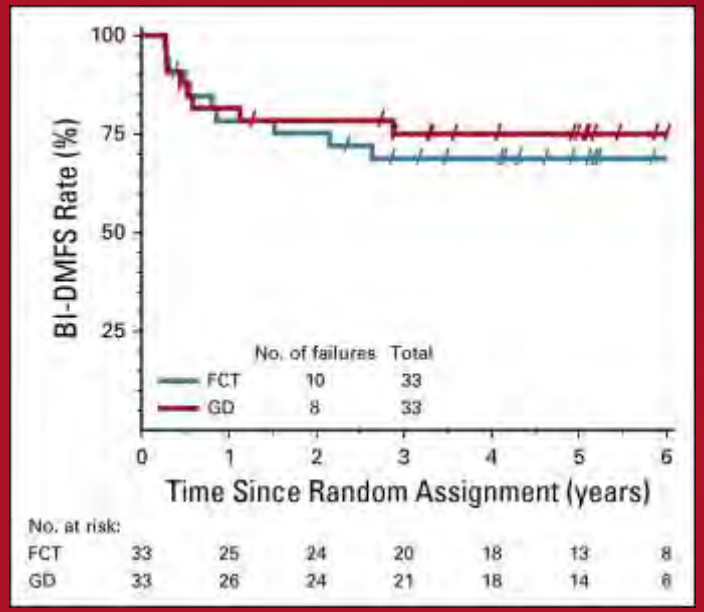


TABLE 3. Adverse Events That Occurred During Treatment by Specific Category (GU, GI, and hematologic toxicities)

	Definitely, Probably, or Possibly Related to Protocol Treatment									
	FCT Arm (n = 33)					GD Arm (n = 33)				
	No. (%) of Patients by Grade					No. (%) of Patients by Grade				
Category	1	2	3	4	5	1	2	3	4	5
Overall highest grade	5 (15.2)	9 (27.3)	12 (36.4)	7 (21.2)	0 (0.0)	9 (27.3)	7 (21.2)	15 (45.5)	2 (6.1)	0 (0.0)
Blood/bone marrow	5 (15.2)	8 (24.2)	11 (33.3)	7 (21.2)	0 (0.0)	14 (42.4)	3 (9.1)	12 (36.4)	2 (6.1)	0 (0.0)
GI	12 (36.4)	15 (45.5)	2 (6.1)	0 (0.0)	0 (0.0)	15 (45.5)	15 (45.5)	3 (9.1)	0 (0.0)	0 (0.0)
Renal/GU	14 (42.4)	5 (15.2)	2 (6.1)	0 (0.0)	0 (0.0)	7 (21.2)	10 (30.3)	2 (6.1)	0 (0.0)	0 (0.0)

NOTE. Adverse events were graded using Common Terminology Criteria for Adverse Events version 3.0. Overall highest grade is based on blood/bone marrow, gastrointestinal, or renal/GU adverse events.

Abbreviations: FCT, fluorouracil plus cisplatin and radiation twice a day; GD, gemcitabine and once daily radiation; GU, genitourinary.

J Clin Oncol. 2019 Jan 1;37(1):44-51.

Current Options for MIBC

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2023
Bladder Cancer

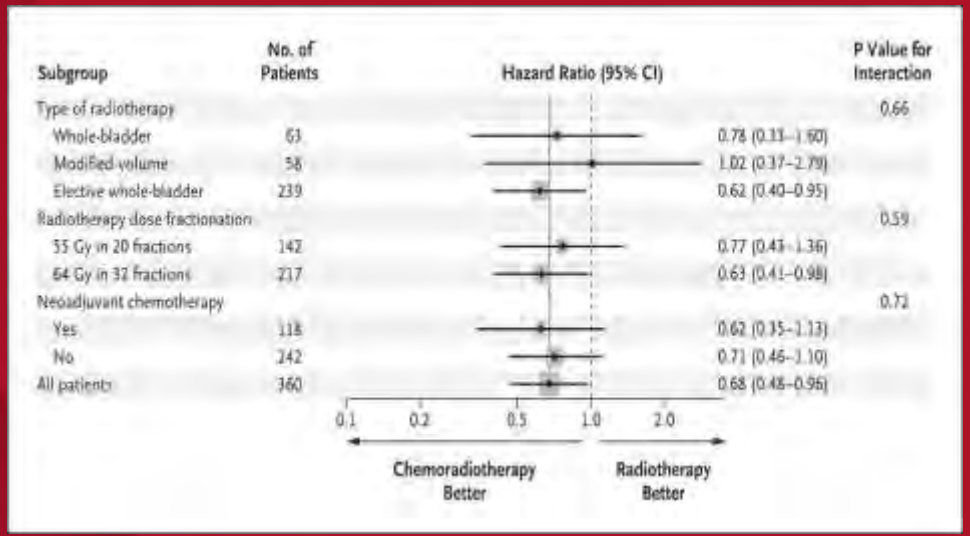
NCCN Guidelines Index
Table of Contents
Discussion

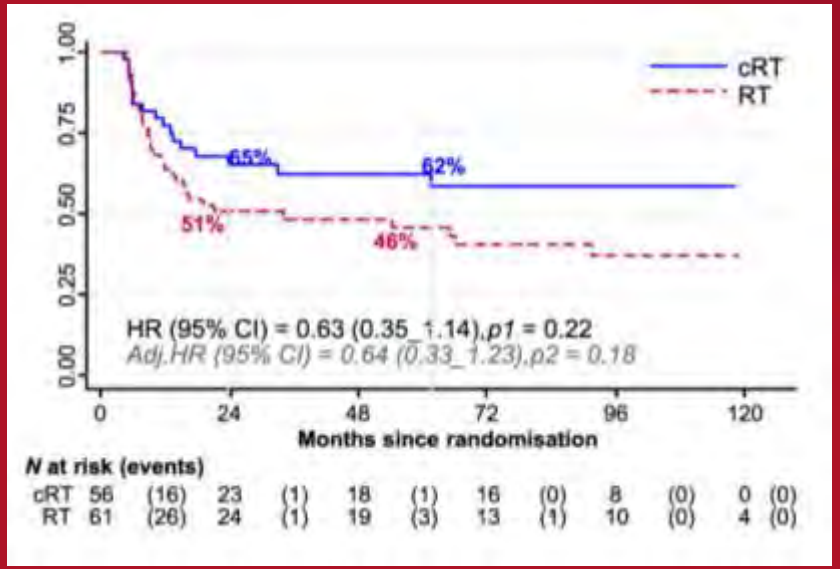
PRINCIPLES OF SYSTEMIC THERAPY

Radiosensitizing Chemotherapy Regimens[i]
Preferred regimens • Cisplatin[h] alone[35,39] • Low-dose gemcitabine[32,36,37] • 5-FU and mitomycin[34]
Other recommended regimen • Cisplatin and 5-FU[31,32] • Cisplatin and paclitaxel[31,33]
Useful in certain circumstances (not generally used for curative-intent chemoradiotherapy for organ preservation) • Taxane (docetaxel or paclitaxel) (category 2B) • 5-FU (category 2B) • Capecitabine (category 3)

Neoadjuvant Chemotherapy

BC2001 Phase 3 Clinical Trial





N Engl J Med 2012;366:1477-1488.

Eur Urol. 2021 Feb;79(2):307-315.

Emerging Options for MIBC

- **Multiple new targeted systemic therapy options now approved**
  - Anti-PD1/L1 antibodies (avelumab, nivolumab, pembrolizumab)
  - Antibody-drug conjugates (enfortumab vedotin, sacituzumab govitecan)
  - FGFR inhibitior (erdafitinib)
  - Combinations (enfortumab vedotin + pembrolizumab)

- **Studies are ongoing incorporates these agents into therapy in localized disease**

Anti-PDL1 + Chemoradiation

Phase 2 study of pembrolizumab + Gemcitabine and radiotherapy

Eligibility (n=54):

- cT2 – cT4a cN0

Therapy:

- Pembrolizumab neoadjuvant and concurrent
- Gemcitabine twice weekly during radiotherapy

Primary Endpoint:

- 2 year bladder intact disease-free survival

Efficacy (n=54)	2-year % (95%CI)	Median in months (range)
BIDFS	71% (69%-91%)	47.4 (33.2-not reached)
MFS	78% (64%-87%)	47.4 (47.4-not reached)
OS	83% (69%-91%)	Not reached
12-week CR rate	80%	NA

Adverse Event	N (%)
Cytopenias	7 (13%)
Colitis/colonic perforation	5 (9%)
Cystitis	2 (4%)
Polyneuropathy	1 (2%)
Fatigue	1 (2%)
Hypokalemia	1 (2%)

J Clin Oncol 41, 2023 (suppl 16; abstr 4509).

Anti-PDL1 + Chemoradiation

Pending Phase 3 studies

NCT # / Study	Intervention	Endpoint
NCT03775265 SWOG 1806	Chemoradiation +/- Atezolizumab	Bladder intact event-free survival
NCT04241185 KEYNOTE-992	Chemoradiation +/- Pembrolizumab	Bladder intact event-free survival
NCT04658862 SunRISe-2	TAR-200 + Cetrelimab vs Chemoradiation	Bladder intact event-free survival

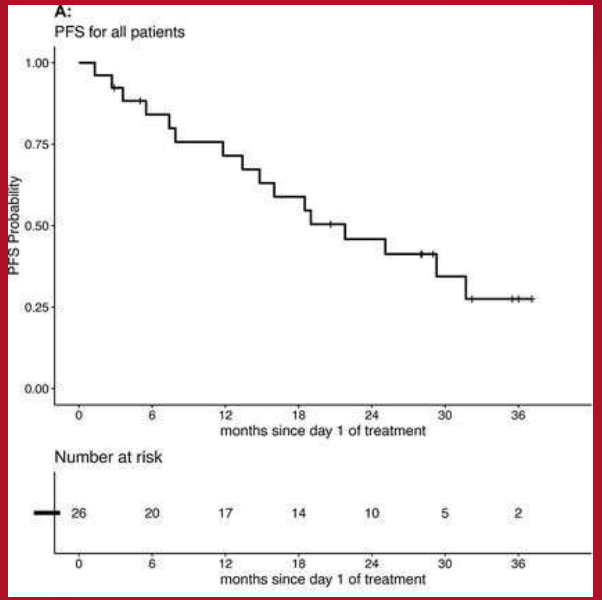
Anti-PDL1 + Radiation alone

Phase 2 study of durvalumab + radiotherapy

Eligibility (n=26):
- cT2-4 cN0-2
- Cisplatin ineligible
- Unfit/unresectable

Therapy:
- Durvalumab concurrent and adjuvant
- Radiotherapy

Primary Endpoint:
- Progression-free survival and disease control rate



Overall response rate: 68.2%

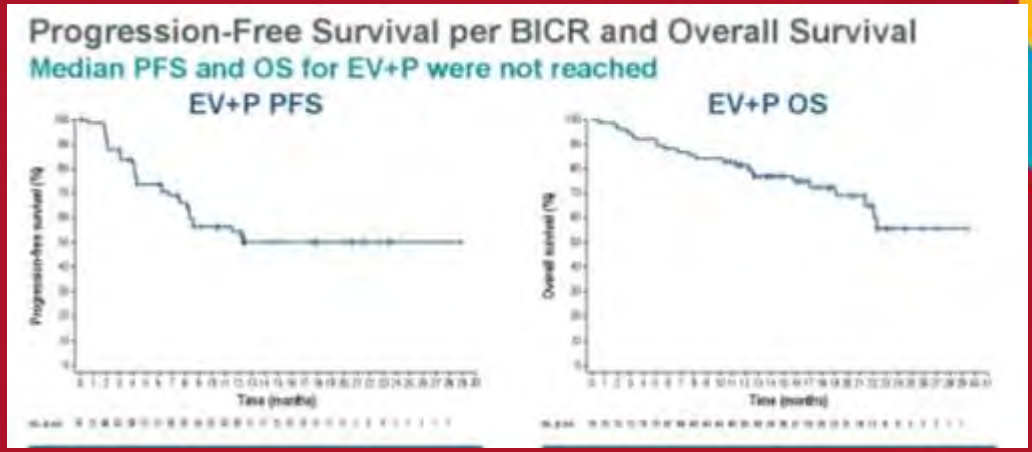
Median PFS: 21.8 months

J Immunother Cancer. 2023 Feb;11(2):e006551.

Other promising agents

Enfortumab vedotin + pembrolizumab

Granted accelerated approval by FDA based upon phase 1-2 study (EV-103) based upon objective response rate (68%)



J Clin Oncol 41, 2023 (suppl 16; abstr 4568).

Key Points

- **Chemotherapy improves outcomes when using radiotherapy in muscle invasive bladder cancer**
  - Definitively improves local control
  - May improve survival
- **Largest study (and only phase 3) used 5FU + Mitomycin**
  - Cisplatin, gemcitabine, other combinations are also options
- **Chemotherapy considerations**
  - Toxicity/Risk increased (IV access, GI toxicity)
  - Neoadjuvant / Adjuvant chemotherapy should be considered

Current approach

Muscle Invasive Bladder Cancer

- If cisplatin eligible, **administer cisplatin-based neoadjuvant chemotherapy**

Primary therapy

- If primary radiotherapy employed, **administer concurrent chemotherapy**

Recurrence?

- Surgery or **palliative systemic therapy**

Future Directions

- **Registrational studies underway of anti-PD1 plus chemoradiation**
  - Expect to incorporate either concurrent or adjuvant immunotherapy into the treatment paradigm
- **Other promising agents yet to be explored**
  - e.g. enfortumab vedotin plus pembrolizumab
- **Any role for treatment without radiotherapy or surgery in muscle-invasive disease?**
  - At least one registrational study underway

Questions?

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