Urinary bladder treatment

Treatment of Non–Muscle-Invasive Bladder Cancer (Ta, Tis, T1)

- Of patients with bladder cancer, 70% have NMIBC.
- Approximately 15% to 20% of these patients will progress to stage T2 disease or greater over time.
- Low-grade tumors (G1 or G2) and low-stage (Ta) disease tend to have a lower recurrence rate at about 50% and a 5% progression rate
- High grade disease (G3, T1 associated with CIS, and multifocal disease) has a 70% recurrence rate and a 30% to 50% progression rate to stage T2 disease or greater.

- The current AUA guidelines for NMIBC risk stratifies patients into low-, intermediate-, and high-risk groups.
- Low risk includes a solitary low-grade tumor 3 cm or smaller.
- Intermediate risk includes a solitary low-grade tumor larger than 3 cm, multifocal low-grade tumors, low-grade tumors that recur within 1 year, solitary highgrade Ta tumors, and low-grade T1 tumors

- High-risk disease includes high-grade T1, any recurrent high-grade Ta, high-grade Ta larger than3 cm or multifocal, any CIS, any recurrence after BCG treatment of a high-grade UC, any variant histology, lymphovascular invasion, or any high-grade prostatic urethral involvement.21

Low-risk NMIBC

- Patients with low-risk NMIBC are managed with TURBT alone or with a single perioperative dose of intravesical chemotherapy given at the conclusion of the procedure as long as there has been no suspicion for bladder perforation.
- Perioperative intravesical chemotherapy has been shown to reduce the risk of recurrence of low-grade disease by up to 35%.
- Mitomycin had previously been the standard of care; however, since the publication of the randomized, double-blind phase III Southwest Oncology Group (SWOG) S0337 clinical trial, gemcitabine has now become the preferred agent because of its lower cost and improved patient tolerability.

Systematic Review and Individual Patient Data Meta-analysis of Randomized Trials Comparing a Single Immediate Instillation of Chemotherapy After Transurethral Resection with Transurethral Resection Alone in Patients with Stage pTa-pT1 Urothelial Carcinoma of the Bladder: Which Patients Benefit from the Instillation?

Sylvester RJ [1], Oosterlinck W [2], Holmang S [3], Sydes MR [4], Birtle A [5], Gudjonsson S [6], De Nunzio C [7], Okamura K [8], Kaasinen E [9], Solsona E [10], Ali-El-Dein B [11], Tatar CA [12], Inman BA [13], N'Dow J [14], Oddens JR [15], Babjuk M [16]

Author information

European Urology, 16 Jun 2015, 69(2):231-244
https://doi.org/10.1016/j.eururo.2015.05.050 PMID: 26091833
Review

Original Investigation FREE

Effect of Intravesical Instillation of Gemcitabine vs Saline Immediately Following Resection of Suspected Low-Grade Non–Muscle-Invasive Bladder Cancer on Tumor Recurrence
SWOG S0337 Randomized Clinical Trial

Edward M. Messing, MD[1]; Catherine M. Tangen, DrPH[2,3]; Seth P. Lerner, MD[4]; et al
Author Affiliations | Article Information

JAMA
Published Online: May 8, 2018
2018;319;(18):1880-1888.
doi:10.1001/jama.2018.4657

Table 2. Primary and Secondary Analysis Comparisons by Treatment Group

Table 2. Primary and Secondary Analysis Comparisons by Treatment Group

Outcomes and Populations	Gemcitabine Group		Saline Group		Hazard Ratio (95% CI)[c]	*P* Value by 1-Sided Log-Rank Test
	No. With Outcome/ Total No.[a]	4-y Recurrence Rate, % (95% CI)[b]	No. With Outcome/ Total No.[a]	4-y Recurrence Rate, % (95% CI)[b]		
Primary Outcome and Primary Population						
Recurrence among all randomized, eligible patients (intention-to-treat population)	67/201	35 (29-42)	91/205	47 (41-54)	0.66 (0.48-0.90)	<.001[d]
Secondary Populations						
Recurrence among all patients who received instillation and had low-grade non-muscle-invasive disease	34/102	34 (26-44)	59/113	54 (45-65)	0.53 (0.35-0.81)	.001[d]
Recurrence among all patients who received instillation and had high-grade non-muscle-invasive disease	17/44	40 (27-58)	19/42	45 (32-63)	0.84 (0.45-1.60)	.38[d]
Secondary Outcomes						
Muscle invasion in intention-to-treat population	5/201		10/205		0.51 (0.17-1.49)	.11
Death due to any cause in intention-to-treat population	17/201		25/205		0.68 (0.37-1.27)	.12

[a] Only a first recurrence for a given patient was counted; number of recurrences represents the number of individuals with a first recurrence.

[b] Four-year event rates were estimated from cumulative incidence curves in which either cystectomy or death prior to recurrence was managed as a competing risk.

[c] Hazard ratios are adjusted for stratification factors as covariates except for time to muscle-invasive disease and survival, which had no adjustment because of low event rates.

[d] Stratified by primary vs recurrent tumor and 1 vs 2 or more tumors.

Intermediate -risk NMIBC

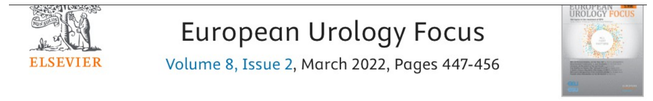
- Patients with intermediate-risk NMIBC should consider treatment with an induction course of 6 weekly intravesical chemotherapy or immunotherapy with BCG. Responders should consider maintenance intravesical therapy for 1 year.
- Intermediate-risk NMIBC is known to be a heterogeneous disease, and the choice between intravesical chemotherapy and BCG is not always straightforward
- A recent meta-analysis in intermediate-risk NMIBC suggests that BCG may not hold any advantage over chemotherapy, and these findings are in line with the authors' practice to first use intravesical chemotherapy in these patients, especially in light of recent BCG shortages.

No Access | Journal of Urology | Adult Urology | 1 Oct 2016

Diagnosis and Treatment of Non-Muscle Invasive Bladder Cancer: AUA/SUO Guideline

Sam S. Chang, Stephen A. Boorjian, Roger Chou, Peter E. Clark, Siamak Daneshmand, Badrinath R. Konety, Raj Pruthi, Diane Z. Quale, Chad R. Ritch, John D. Seigne, Eila Curlee Skinner, Norm D. Smith, and James M. McKiernan
View All Author Information

https://doi.org/10.1016/j.juro.2016.06.049



Review – Bladder Cancer

Intravesical Therapy in Patients with Intermediate-risk Non–muscle-invasive Bladder Cancer: A Systematic Review and Network Meta-analysis of Disease Recurrence

Ekaterina Laukhtina [a b †], Mohammad Abufaraj [a c †], Abdallah Al-Ani [c], Mustafa Rami Ali [c], Keiichiro Mori [a d], Marco Moschini [a e f], Fahad Quhal [a g], Reza Sari Motlagh [a h], Benjamin Pradere [a], Victor M. Schuettfort [a i], Hadi Mostafaei [a j], Satoshi Katayama [a k], Nico C. Grossmann [a l], Harun Fajkovic [a m], Francesco Soria [n], Dmitry Enikeev [b], Shahrokh F. Shariat [a b c m o p q], European Association of Urology-Young Academic Urologists (EAU-YAU): Urothelial carcinoma working group

High-risk NMIBC

- In high-risk NMIBC, after undergoing repeat TURBT to assure no occult MIBC and no residual disease, one should strongly consider treatment with intravesical BCG.
- Intravesical BCG therapy is typically initiated with an induction course of 6 weekly instillations, and for those who respond to induction, maintenance BCG therapy for up to 3 years is a standard of care.
- In recent years, there have been national shortages of BCG for intravesical therapy, necessitating professional urologic oncologic organizations to recommend limiting its use in only the highest risk patients, including those with high-grade T1 disease or CIS.
- In addition, although full-dose BCG should be used for induction, a half or one-third dose could be considered for maintenance therapy.

No Access | Journal of Urology | CLINICAL UROLOGY: Original Articles | 1 Apr 2000

MAINTENANCE BACILLUS CALMETTE-GUERIN IMMUNOTHERAPY FOR RECURRENT TA, T1 AND CARCINOMA IN SITU TRANSITIONAL CELL CARCINOMA OF THE BLADDER: A RANDOMIZED SOUTHWEST ONCOLOGY GROUP STUDY

DONALD L. LAMM, BRENT A. BLUMENSTEIN, JOHN D. CRISSMAN, JAMES E. MONTIE, JAMES E. GOTTESMAN, BRUCE A. LOWE, MICHAEL F. SAROSDY, ROBERT D. BOHL, H. BARTON GROSSMAN, THOMAS M. BECK, JOSEPH T. LEIMERT, and E. DAVID CRAWFORD
View All Author Information

https://doi.org/10.1016/S0022-5347(05)67707-5

PRINCIPLES OF INSTILLATION THERAPY

Indications: Based on probability of recurrence and progression to muscle-invasive disease, such as size, number, and grade.

Intravesical Therapy for Bladder Cancer

Immediate Postoperative Intravesical Chemotherapy

- **Clinical Presentation and Initial Evaluation (BL-1)**
- **A single instillation of chemotherapy is administered within 24 hours of surgery (ideally within 6 hours).**
- **Gemcitabine (category 1) (preferred)[1] and mitomycin (category 1)[2] are the most commonly used agents in the United States for intravesical chemotherapy. Thiotepa does not appear to be effective.[3]**
- **Immediate postoperative intravesical chemotherapy reduces the 5-year recurrence rate by approximately 35% and has a number needed to treat to prevent a recurrence of 7. However, it does not reduce the risk of progression or the risk of cancer mortality.[3]**
- **It is not effective in patients with an elevated EORTC recurrence risk score (≥5). This includes patients with ≥8 tumors and those with ≥1 recurrence per year.**
- **Most efficacious in patients with low-grade, low-volume Ta urothelial cancer.**
- **Contraindications include: bladder perforation, known drug allergy.**

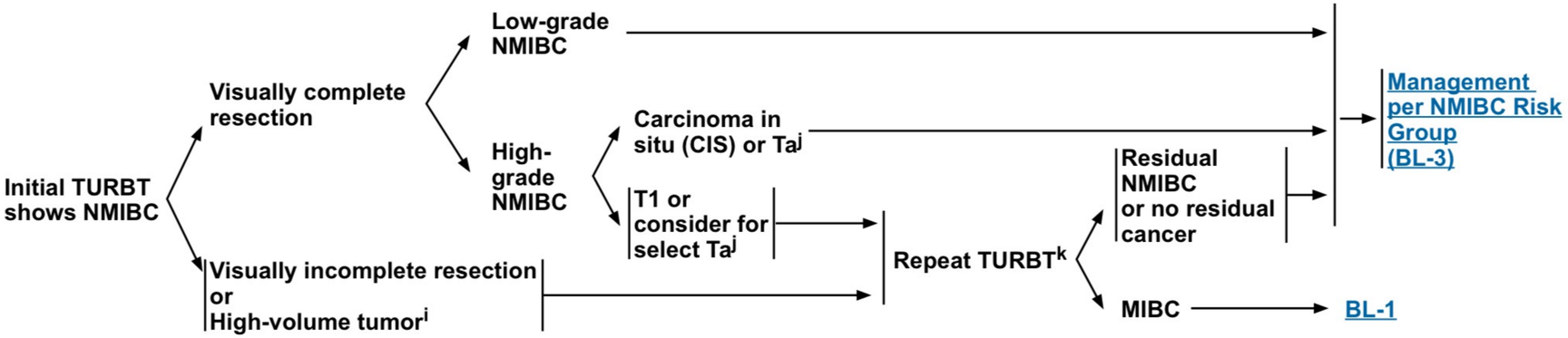
Induction (Adjuvant) Intravesical Chemotherapy or BCG

- **Treatment option for NMIBC.**
- **The most commonly used agents are BCG, mitomycin, and gemcitabine.**
- **Initiated 3–4 weeks after TURBT with or without maintenance.**
- **Weekly instillations during induction are given for approximately 6 weeks.**
- **Maximum of 2 consecutive cycle inductions without complete response.**
- **Withhold if traumatic catheterization, bacteriuria, persistent gross hematuria, persistent severe local symptoms, or systemic symptoms.**

Maintenance Intravesical BCG

- **Although there is no standard regimen for maintenance BCG, many NCCN Member Institutions follow the SWOG regimen consisting of a 6-week induction course of BCG followed by maintenance with 3 weekly instillations at months 3, 6, 12, 18, 24, 30, and 36.[4]**
- **Ideally maintenance should be given for 1 year for intermediate-risk and 3 years for high-risk NMIBC.**
- **BCG would be withheld if traumatic catheterization, bacteriuria, persistent gross hematuria, persistent severe local symptoms, or systemic symptoms.**
- **Dose reduction is encouraged if there are substantial local symptoms during maintenance therapy.**
- **Data suggest the benefit of maintenance BCG therapy through a decreased rate of recurrence for NMIBC.[4]**

RISK STRATIFICATION OF NMIBC



AUA Risk Stratification for Non–Muscle-Invasive Bladder Cancer*

Low Risk	Intermediate Risk	High Risk
• Papillary urothelial neoplasm of low malignant potential • Low grade urothelial carcinoma ‣ Ta and ‣ ≤3 cm and ‣ Solitary	• Low grade urothelial carcinoma ‣ T1 or ‣ >3 cm or ‣ Multifocal or ‣ Recurrence within 1 year • High grade urothelial carcinoma ‣ Ta and ‣ ≤3 cm and ‣ Solitary	• High grade urothelial carcinoma ‣ CIS or ‣ T1 or ‣ >3 cm or ‣ Multifocal • Very high risk features (any): ‣ BCG unresponsive[l] ‣ Certain histopathologic subtypes[m] ‣ Lymphovascular invasion ‣ Prostatic urethral invasion

Adapted with permission from Chang SS, Boorjian SA, Chou R, et al. Diagnosis and treatment of non-muscle invasive bladder cancer: AUA/SUO guideline. J Urol 2016;196:1021-1029.

*Within each of these risk strata an individual patient may have more or fewer concerning features that can influence care.

[i] High-volume tumors (large or highly multifocal) are at high risk of residual tumor.
[j] Consider repeat TURBT for high-grade Ta particularly if large, and/or no muscle in specimen.
[k] Muscle should be present in repeat TURBT pathology specimen if possible.

[l] Kamat AM, et al. J Clin Oncol 2016;34:1935-1944.
[m] See aggressive subtype histologies listed on Bladder Cancer: Non-Urothelial and Urothelial with Subytpe Histology (BL-D).

Note: All recommendations are category 2A unless otherwise indicated.

The University Of Sheffield.

Risk Stratification

Weighting factors for recurrence and progression scores

Factor	Recurrence	Progression
Number of tumors		
Single	0	0
2 to 7	3	3
≥8	6	3
Tumor size		
<3 cm	0	0
≥3 cm	3	3
Prior recurrence rate		
Primary	0	0
≤1 rec/yr	2	2
>1 rec/yr	4	2
T category		
Ta	0	0
T1	1	4
CIS		
No	0	0
Yes	1	6
Grade		
G1	0	0
G2	1	0
G3	2	5
Total score	0–17	0–23

Probability (range) of recurrence and progression per 1 and 5 years

Recurrence score	Prob recurrence 1 year (95% CI)	Prob recurrence 5 years (95% CI)
0	15% (10%, 19%)	31% (24%, 37%)
1–4	24% (21%, 26%)	46% (42%, 49%)
5–9	38% (35%, 41%)	62% (58%, 65%)
10–17	61% (55%, 67%)	78% (73%, 84%)
Progression score	**Prob progression 1 year (95% CI)**	**Prob progression 5 years (95% CI)**
0	0.2% (0%, 0.7%)	0.8% (0%, 1.7%)
2–6	1.0% (.4%, 1.6%)	6% (5%, 8%)
7–13	5% (4%, 7%)	17% (14%, 20%)
14–23	17% (10%, 24%)	45% (35%, 55%)

2596 patients from seven EORTC trials

For references, see text.

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2025
Non–Muscle-Invasive Bladder Cancer

NCCN Guidelines Index
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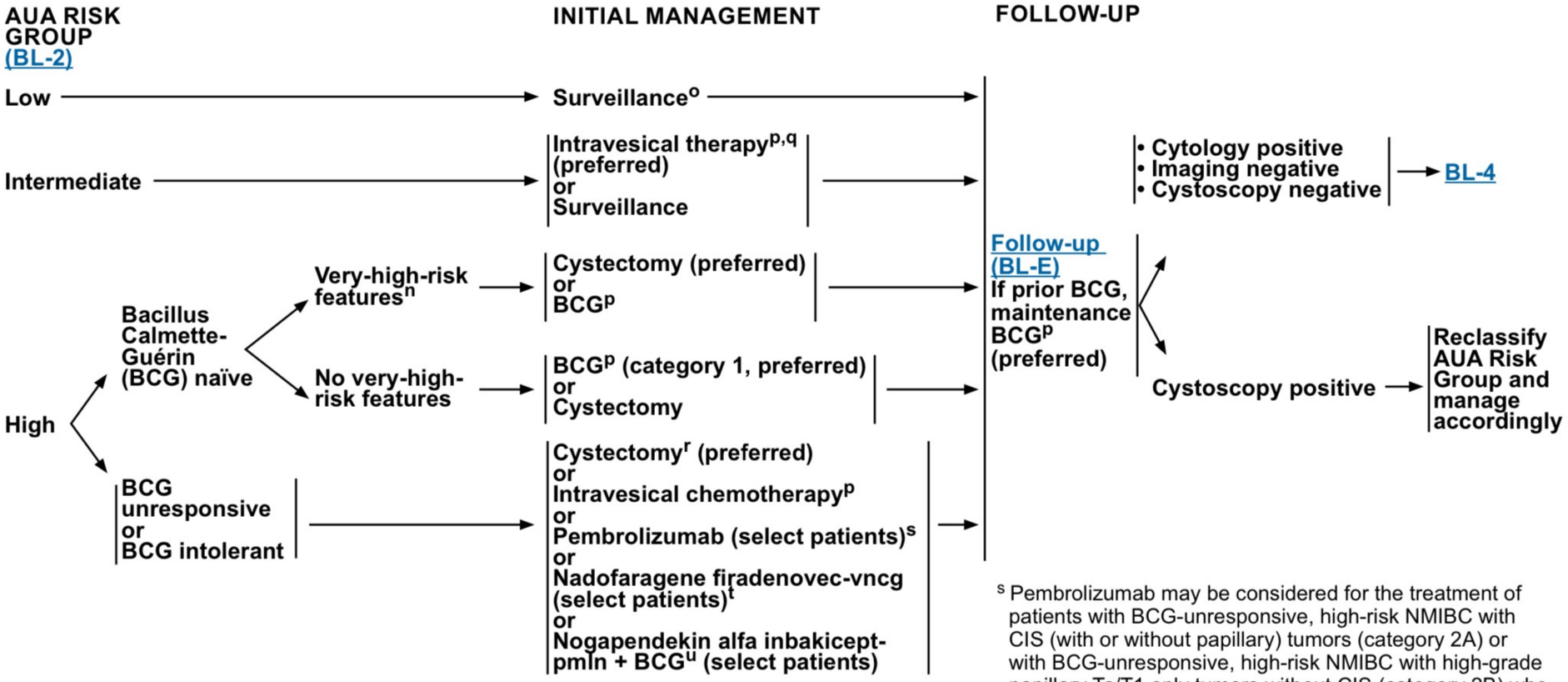
Discussion

MANAGEMENT PER NMIBC RISK GROUP

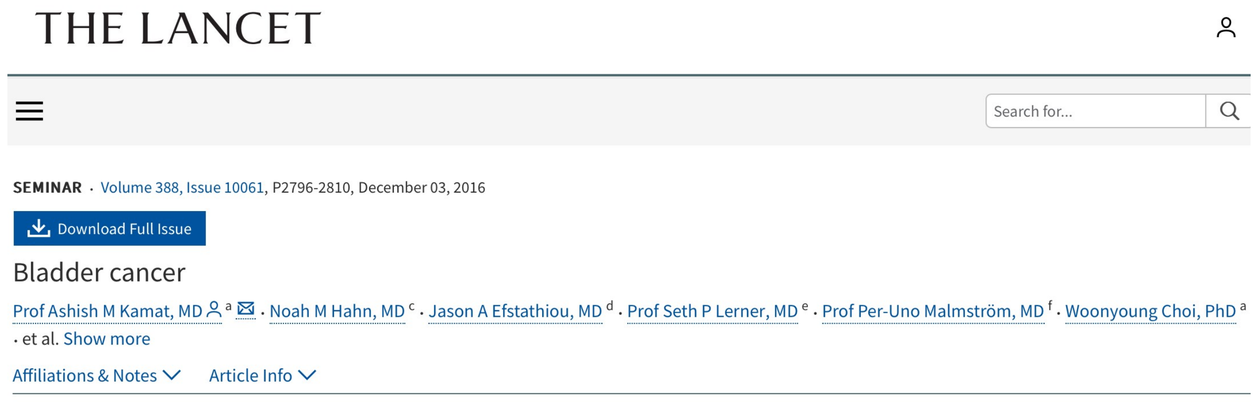


[n] Lymphovascular invasion, prostatic urethral involvement of tumor, subtype histology (eg, micropapillary, plasmacytoid, sarcomatoid).
[o] Should consider single perioperative instillation of intravesical chemotherapy at time of TURBT.
[p] Principles of Instillation Therapy (BL-F).
[q] Options for intravesical therapy for intermediate-risk disease include BCG and chemotherapy; should consider BCG availability in decision-making.
[r] If not a cystectomy candidate, and recurrence is high-grade cTa or cT1, consider concurrent chemoradiotherapy (category 2B for cTa, category 2A for cT1) or a clinical trial. See Principles of Systemic Therapy (BL-G 5 of 7).
[s] Pembrolizumab may be considered for the treatment of patients with BCG-unresponsive, high-risk NMIBC with CIS (with or without papillary) tumors (category 2A) or with BCG-unresponsive, high-risk NMIBC with high-grade papillary Ta/T1 only tumors without CIS (category 2B) who are ineligible for or have elected not to undergo cystectomy.
[t] Nadofaragene firadenovec-vncg may be considered for the treatment of patients with BCG-unresponsive, high-risk, NMIBC with CIS (with or without papillary) (category 2A) or with BCG-unresponsive, high-risk, NMIBC with high-grade papillary Ta/T1 only tumors without CIS (category 2B).
[u] Nogapendekin alfa inbakicept-pmln in combination with BCG may be considered for the treatment of patients with BCG-unresponsive, high-risk NMIBC with CIS (with or without papillary) tumors.

Note: All recommendations are category 2A unless otherwise indicated.

BCG failure/refractory tumor

- The precise definitions of BCG failure are well defined and include four subtypes of BCG failure:
- (1) BCG refractory, which is persistent high-grade disease at less than 6 months after an “adequate” course of induction and one cycle of maintenance
- (2) BCG relapsing, which is recurrence of high-grade disease after a disease-free interval of 6 months or more after “adequate” BCG
- (3) BCG unresponsive, which is a category developed for clinical trial design and includes the BCG refractory and relapsing
- (4) BCG intolerant, which is disease persistence caused by the patient’s inability to tolerate “adequate” BCG because of side effects. The BCG-unresponsive group represent those at greatest risk for disease recurrence and progression.
- BCG-refractory T1 disease should be of paramount concern for understaged disease and should prompt a strong consideration of radical cystectomy.



- Although cystectomy remains the standard for BCG-refractory T1 disease, the single-arm phase II RTOG 0926 study evaluated chemoradiation for bladder preservation in such patients who opt for an attempt at bladder preservation or were otherwise not good cystectomy candidates.
- This trial demonstrated an 88% cystectomy-free survival rate at 3 years; however, the overall survival rate was only 69% and likely underscored the age and comorbidity of this population.
- Options for further intravesical treatment after BCG failure include BCG plus interferon-α, valrubicin, gemcitabine, docetaxel, and other novel agents.
- Intravesical combination chemotherapy with gemcitabine and docetaxel has become a popular option in recent years with the initial data suggesting a 34% disease-free rate at 2 years and a more recent multi-institutional retrospective study demonstrating 1 and 2 year high-grade recurrence-free survival rates of 65% and 52%, respectively.

1078 · Volume 111, Issue 3, Supplement , S133-S134, November 01, 2021

NRG Oncology/RTOG 0926: Phase II Protocol for Patients With Stage T1 Bladder Cancer to Evaluate Selective Bladder Preserving Treatment by Radiation Therapy Concurrent With Radiosensitizing Chemotherapy Following a Thorough Transurethral Surgical Re-Staging

D.M. Dahl [1] · J. Rodgers [2] · W.U. Shipley [3] · ... · D.E. Citrin [12] · T.G. Karrison [13] · F.Y. Feng [14] ... Show more

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First published online April 30, 2015

Sequential Intravesical Gemcitabine and Docetaxel for the Salvage Treatment of Non-Muscle Invasive Bladder Cancer

Ryan L. Steinberg, Lewis J. Thomas, [...], and Kenneth G. Nepple +1 View all authors and affiliations

No Access | Journal of Urology | Adult Urology | 1 May 2020

Multi-Institution Evaluation of Sequential Gemcitabine and Docetaxel as Rescue Therapy for Nonmuscle Invasive Bladder Cancer

- Systemic immunotherapy with pembrolizumab has been evaluated in patients with recurrent NMIBC despite BCG.
- The activated programmed death-1 (PD-1) signaling pathway has been implicated in resistance to BCG. Pembrolizumab is an antibody that inhibits PD-1 signaling.
- In a phase 2 study, 101 patients with BCG-unresponsive CIS with or without papillary tumors were assigned to receive 200 mg of pembrolizumab intravenously every 3 weeks for up to 24 months.89
- The primary endpoint was clinical complete response (CR) rate at 3 months. Of 96 evaluable patients, 41% had a CR at 3 months, with a median duration of CR of 16.2 months.

ARTICLES · Volume 22, Issue 7, P919-930, July 2021

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Pembrolizumab monotherapy for the treatment of high-risk non-muscle-invasive bladder cancer unresponsive to BCG (KEYNOTE-057): an open-label, single-arm, multicentre, phase 2 study

Prof Arjun V Balar, MD [a] · Prof Ashish M Kamat, MD [b] · Girish S Kulkarni, MD [c] · Prof Edward M Uchio, MD [d] · Joost L Boormans, MD [e] · Mathieu Roumiguié, MD [f] · et al.
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Affiliations & Notes · Article Info

- Approximately 15% of patients with NMIBC at high risk for disease progression (CIS with associated Ta or T1 disease, rapidly recurrent disease, or high-grade disease), irrespective of treatment modality, will ultimately die of their disease.
- In addition, up to 16% of patients with high-grade T1 disease may have microscopic lymph node involvement at the time of surgery.
- These investigations identified that in patients with high-grade T1 disease, tumor size 3 cm or greater, the presence of concomitant CIS, deep lamina propria invasion, and lymphovascular invasion are the most significant risk factors for progression to invasive disease and cancer-specific survival.

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SUPERFICIAL BLADDER CARCINOMA TREATED WITH BACILLUS CALMETTE-GUERIN: PROGRESSION-FREE AND DISEASE SPECIFIC SURVIVAL WITH MINIMUM 10-YEAR FOLLOWUP

JOHN W. DAVIS, SEEMIT I. SHETH, MICHAEL J. DOVIAK, and PAUL F. SCHELLHAMMER
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International Cohor

Martin Fritsche [a], Maximilian Burger [a]

European Urology
Volume 67, Issue 1, January 2015, Pages 74-82

Platinum Priority – Urothelial Cancer
Editorial by David R. Yates on pp. 83–84 of this issue

Prognostic Factors and Risk Groups in T1G3 Non–Muscle-invasive Bladder Cancer Patients Initially Treated with Bacillus Calmette-Guérin: Results of a Retrospective Multicenter Study of 2451 Patients

Paolo Gontero [a], Richard Sylvester [b],

Treatment of Muscle-Invasive Disease

- Radical cystectomy is the standard of care for patients with all primary bladder histologies that invade the muscularis propria of the bladder.
- In men, the procedure includes en bloc removal of theprostate.
- Complete urethrectomy may also be required if there is found to be neoplasia or dysplasia distal to the prostatic urethra. When the prostate stroma is involved with UC or when there is concomitant CIS of the urethra, a cystoprostatourethrectomy is the treatment of choice.
- In women, an anterior exenteration is performed.
- This includes en bloc removal of the bladder and urethra, the ventral vaginal wall, and the uterus.
- In some cases, for women with tumor sufficiently distant from the vagina, a vaginal-sparing and uterine-sparing approach may be considered to reduce the impact of sexual dysfunction resulting from anterior exenteration.
- The urethra may be spared in men or women if the urinary diversion chosen is a neobladder.
- In all radical cystectomy surgery, an extended pelvic lymph node dissection should be performed.

Witjes JA, Bruins HM, Cathomas R, Compérat EM, Cowan NC, Gakis G, Hernández V, Espinós EL, Lorch A, Neuzillet Y, Rouanne M. European Association of Urology guidelines on muscle-invasive and metastatic bladder cancer: summary of the 2020 guidelines. European urology. 2021 Jan 1;79(1):82-104.

- Partial cystectomy may rarely be appropriate, thus preserving bladder function and affording in the properly selected patient the same cure rate as a radical cystectomy.
- Patients who are candidates for such procedures must have focal disease located far enough away from the ureteral orifices and bladder neck to achieve at least a 2-cm margin around the tumor and a margin sufficient around the ureteral orifices and bladder neck to reconstruct the bladder.
- Practically, this limits partial cystectomy to rare patients who have small tumors located in the dome of the bladder and in whom random bladder biopsies show no evidence of diffuse CIS or other bladder tumors.

No Access | Journal of Urology | Adult Urology | 1 Oct 2012

Does Partial Cystectomy Compromise Oncologic Outcomes for Patients with Bladder Cancer Compared to Radical Cystectomy? A Matched Case-Control Analysis

John J. Knoedler, Stephen A. Boorjian, Simon P. Kim, Christopher J. Weight, Prabin Thapa, Robert F. Tarrell, John C. Cheville, and Igor Frank
View All Author Information

https://doi.org/10.1016/j.juro.2012.06.029

- Minimally invasive approaches to cystectomy have become increasingly popular.
- In two randomized trials, there were no significant differences in outcomes between standard open cystectomy and robotic-assisted laparoscopic surgery.

Neoadjuvant Therapy

- The advantage of neoadjuvant chemotherapy is its potential to downsize and downstage tumors and to attack occult metastatic disease early, especially given the frequent postoperative complications and prolonged recovery that can delay or derail plans for adjuvant chemotherapy.

- The disadvantages of neoadjuvant therapy include the inherent difficulties in assessing response, the fact that clinical rather than pathologic criteria must be relied on, the debilitating effects of chemotherapy in some patients, increasing the risks of surgery, and the possibility of deleterious effects of the delay in cystectomy or definitive radiation.

- The study by Grossman et al. randomly assigned patients with MIBC (stage T2–T4a) to radical cystectomy alone or three cycles of MVAC followed by radical cystectomy. During an 11-year period, 317 patients were enrolled.
- The survival benefit associated with MVAC appeared to be strongly related to downstaging of the tumor to pT0. Of the chemotherapy-treated patients, 38% had no evidence of cancer at cystectomy compared with 15% of patients in the cystectomy-only group. In both groups, improved OS was associated with the absence of residual cancer in the cystectomy specimen.
- The median OS period was 77 months for the chemotherapy-treated patients compared with 46 months for the cystectomy-only group.
- The 5-year survival rate was 43% in the cystectomy group, which was not significantly different from 57% in the chemotherapy-treated group
- Stratification by tumor stage indicated greater improvement in median OS with chemotherapy in participants with T3 to T4a disease (65 vs 24 months, chemotherapy vs observation) than in subjects with T2 disease (105 vs 75 months).

Grossman HB, Natale RB, Tangen CM, Speights VO, Vogelzang NJ, Trump DL, White RW, Sarosdy MF, Wood Jr DP, Raghavan D, Crawford ED. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. New England Journal of Medicine. 2003 Aug 28;349(9):859-66.

- The Medical Research Council and the (EORTC) performed a prospective randomized trial of neoadjuvant cisplatin, methotrexate, and vinblastine (CMV) in patients undergoing cystectomy or full-dose external-beam radiotherapy for MIBC.
- In the initial report with a median follow-up period of 7.4 years, the difference in 5-year survival between those who received chemotherapy (49%) and those who did not (43%) just reached clinical significance with a probability value of 0.048.
- The survival benefit did not reach the prespecified study goal.
- Long-term follow-up of the study with median follow-up of 8 years and more death events demonstrated that systemic chemotherapy plus local treatment improved the 10-year OS rate by 6% and reduced the risk of bladder cancer death by 17% compared with local treatment alone.

ELSEVIER

The Lancet

Volume 354, Issue 9178, 14 August 1999, Pages 533-540

Articles

Neoadjuvant cisplatin,methotrexate,and vinblastine chemotherapy for muscle-invasive bladder cancer: a randomised controlled trial

International collaboration of trialists on behalf of the Medical Research Council Advanced Bladder Cancer Working Party
, EORTC Genito-Urinary Group, Australian Bladder Cancer Study Group, National Cancer Institute of Canada Clinical Trials Group, Finnbladder, Norwegian Bladder Cancer Study Group, Club Urologico Espanol de Tratamiento Oncologico (CUETO) group

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International Phase III Trial Assessing Neoadjuvant Cisplatin, Methotrexate, and Vinblastine Chemotherapy for Muscle-Invasive Bladder Cancer: Long-Term Results of the BA06 30894 Trial

Author: International Collaboration of Trialists on behalf of the Medical Research Council Advanced Bladder Cancer Working Party (now the National Cancer Research Institute Bladder Cancer Clinical Studies Group), the European Organisation for Research and Treatment of Cancer Genito-Urinary Tract Cancer Group, the Australian Bladder Cancer Study Group, the National Cancer Institute of Canada Clinical Trials Group, Finnbladder, Norwegian Bladder Cancer Study Group, and Club Urologico Espanol de Tratamiento Oncologico Group | AUTHORS INFO & AFFILIATIONS

Publication: Journal of Clinical Oncology • Volume 29, Number 16 • https://doi.org/10.1200/JCO.2010.32.3139

- A third randomized trial was the Nordic Cystectomy Trial 1.
- The Nordic Cooperative Bladder Cancer Study Group conducted a randomized phase III study to assess the possible benefit of neoadjuvant chemotherapy in patients with bladder cancer undergoing radical cystectomy.
- trial included 325 patients with locally advanced stage T1 grade 3 or stages T2 to T4aNXMO bladder cancer allocated randomly
- Patients were treated with two cycles of neoadjuvant doxorubicin and cisplatin.
- All patients received 5 days of radiation followed by cystectomy.
- A subgroup analysis showed a 20% difference in DSS at 5 years in patients with T3 and T4 disease, but there was no difference in stages T1 and T2, nor a difference when all entered patients were compared.

- Many phase II studies have investigated alternative neoadjuvant combinations, including GC and dose-dense MVAC.
- Dose-dense MVAC (ddMVAC), accelerated MVAC (AMVAC), and high-dose intensity MVAC (HD-MVAC) are nearly synonymous terms for MVAC that is given on a compressed schedule over 14 days rather than the standard 28 days.
- Doses of doxorubicin and cisplatin remain the same, but the doses of methotrexate and vinblastine on days 15 and 22 are omitted, effectively doubling the administered dose of doxorubicin and cisplatin in half the time for standard MVAC.

Journal of Clinical Oncology®
An American Society of Clinical Oncology Journal

CURRENT I

PARTIAL ACCESS | ORIGINAL REPORTS | May 12, 2014

Accelerated Methotrexate, Vinblastine, Doxorubicin, and Cisplatin Is Safe, Effective, and Efficient Neoadjuvant Treatment for Muscle-Invasive Bladder Cancer: Results of a Multicenter Phase II Study With Molecular Correlates of Response and Toxicity

Authors: Elizabeth R. Plimack, Jean H. Hoffman-Censits, Rosalia Viterbo, Edouard J. Trabulsi, Eric A. Ross, Richard E. Greenberg, David Y.T. Chen, ... SHOW ALL ... , and Gary R. Hudes | AUTHORS INFO & AFFILIATIONS

Publication: Journal of Clinical Oncology • Volume 32, Number 18 • https://doi.org/10.1200/JCO.2013.53.2465

- EORTC protocol 30924 was a randomized phase III trial that demonstrated improved response rate, PFS, and OS for ddMVAC compared with standard MVAC in the metastatic setting.
- After a median follow-up of 7.3 years, 24.6% are alive on the HD-M-VAC arm vs. 13.2% on the M-VAC arm.
- Median progression-free survival was better with HD-MVAC (9.5 months) vs. M-VAC (8.1 months).
- The mortality hazard ratio (HR) was 0.76.
- The 2-year survival rate for HD-M-VAC was 36.7% vs. 26.2% for M-VAC. At 5 years, the survival rate was 21.8% in the HD-M-VAC vs. 13.5%. Median survival was 15.1 months on HD-MVAC and 14.9 months on M-VAC.

Journal of Clinical Oncology®
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CURRENT IS

ORIGINAL REPORTS | May 15, 2001

Randomized Phase III Trial of High–Dose-Intensity Methotrexate, Vinblastine, Doxorubicin, and Cisplatin (MVAC) Chemotherapy and Recombinant Human Granulocyte Colony-Stimulating Factor Versus Classic MVAC in Advanced Urothelial Tract Tumors: European Organization for Research and Treatment of Cancer Protocol No. 30924

Authors: C. N. Sternberg, P. H.M. de Mulder, J. H. Schornagel, C. Théodore, S. D. Fossa, A. T. van Oosterom, F. Witjes, M. Spina, C. J. van Groeningen, C. de Balincourt, L. Collette, and for the European Organization for Research and Treatment of Cancer Genitourinary Tract Cancer Cooperative Group | AUTHORS INFO & AFFILIATIONS

Publication: Journal of Clinical Oncology • Volume 19, Number 10 • https://doi.org/10.1200/JCO.2001.19.10.2638

- In the neoadjuvant setting, ddMVAC was tolerable and associated with pathologic T0 rates comparable to standard MVAC.
- Patients with cT2-cT4, N0-1, M0 MIUC were enrolled. Four cycles of ddMVAC were administered, followed by radical cystectomy.
- Between December 2008 and April 2012, 39 patients (cT2N0, 33%; cT3N0, 18%; cT4N0, 3%; cT2-4N1, 43%; unspecified, 3%) were enrolled. Median follow-up was 2 years. Overall, 49% (80% CI, 38 to 61) achieved PaR of ≤ pT1N0M0, and we concluded this regimen was effective.
- One-year DFS was 89% versus 67% for patients who achieved PaR compared with those who did not (P = .08) and 86% versus 62% for patients who achieved RaR compared with those who did not (P = .009)
- Despite the absence of phase III randomized data to support its use in the neoadjuvant setting, ddMVAC has become a preferred regimen over standard MVAC.

Journal of Clinical Oncology®
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CURRENT ISSU

PARTIAL ACCESS | ORIGINAL REPORTS | May 12, 2014

Neoadjuvant Dose-Dense Methotrexate, Vinblastine, Doxorubicin, and Cisplatin With Pegfilgrastim Support in Muscle-Invasive Urothelial Cancer: Pathologic, Radiologic, and Biomarker Correlates

Authors: Toni K. Choueiri, Susanna Jacobus, Joaquim Bellmunt, Angela Qu, Leonard J. Appleman, Christopher Tretter, Glenn J. Bubley, ... SHOW ALL ... , and Jonathan E. Rosenberg | AUTHORS INFO & AFFILIATIONS

Publication: Journal of Clinical Oncology • Volume 32, Number 18 • https://doi.org/10.1200/JCO.2013.52.4785

- The SWOG 1314 study was a randomized controlled trial comparing ddMVAC with GC neoadjuvant chemotherapy and demonstrated comparable rates of achieving pT0 at cystectomy (28% and 30%, respectively; P = 0.75).

CLINICAL TRIALS: TARGETED THERAPY | MAY 01 2021

A Randomized Phase II Study of Coexpression Extrapolation (COXEN) with Neoadjuvant Chemotherapy for Bladder Cancer (SWOG S1314; NCT02177695)

Thomas W. Flaig; Catherine M. Tangen; Siamak Daneshmand; Ajjai Alva; Seth P. Lerner; M. Scott Lucia; David J. McConkey; Dan Theodorescu; Amir Goldkorn; Matthew I. Milowsky; Rick Bangs; Gary R. MacVicar; Bruno R. Bastos; Jared S. Fowles; Daniel L. Gustafson; Melissa Plets; Ian M. Thompson, Jr

+ Author & Article Information

Clin Cancer Res (2021) 27 (9): 2435–2441.

Sandwich therapy

- In this phase 3, open-label, randomized trial, we assigned, in a 1:1 ratio, cisplatin-eligible patients with muscle-invasive bladder cancer to receive neoadjuvant durvalumab plus gemcitabine–cisplatin every 3 weeks for four cycles, followed by radical cystectomy and adjuvant durvalumab every 4 weeks for eight cycles (durvalumab group), or to receive neoadjuvant gemcitabine–cisplatin followed by radical cystectomy alone (comparison group).
- The estimated event-free survival at 24 months was 67.8% in the durvalumab group and 59.8% in the comparison group.
- The estimated overall survival at 24 months was 82.2% in the durvalumab group and 75.2% in the comparison group.

ORIGINAL ARTICLE

Perioperative Durvalumab with Neoadjuvant Chemotherapy in Operable Bladder Cancer

Authors: Thomas Powles, M.D., James W.F. Catto, Ph.D., F.R.C.S.(Urol.), Matthew D. Galsky, M.D., Hikmat Al-Ahmadie, M.D., Joshua J. Meeks, M.D., Ph.D., Hiroyuki Nishiyama, M.D., Ph.D., Toan Quang Vu, M.D., +18, for the NIAGARA Investigators* Author Info & Affiliations

Published September 15, 2024 | **N Engl J Med 2024;391:1773-1786**
DOI: 10.1056/NEJMoa2408154 | **VOL. 391 NO. 19** | **Copyright © 2024**

NCCN Guidelines Version 1.2025
Muscle-Invasive Bladder Cancer

NCCN Guidelines Index
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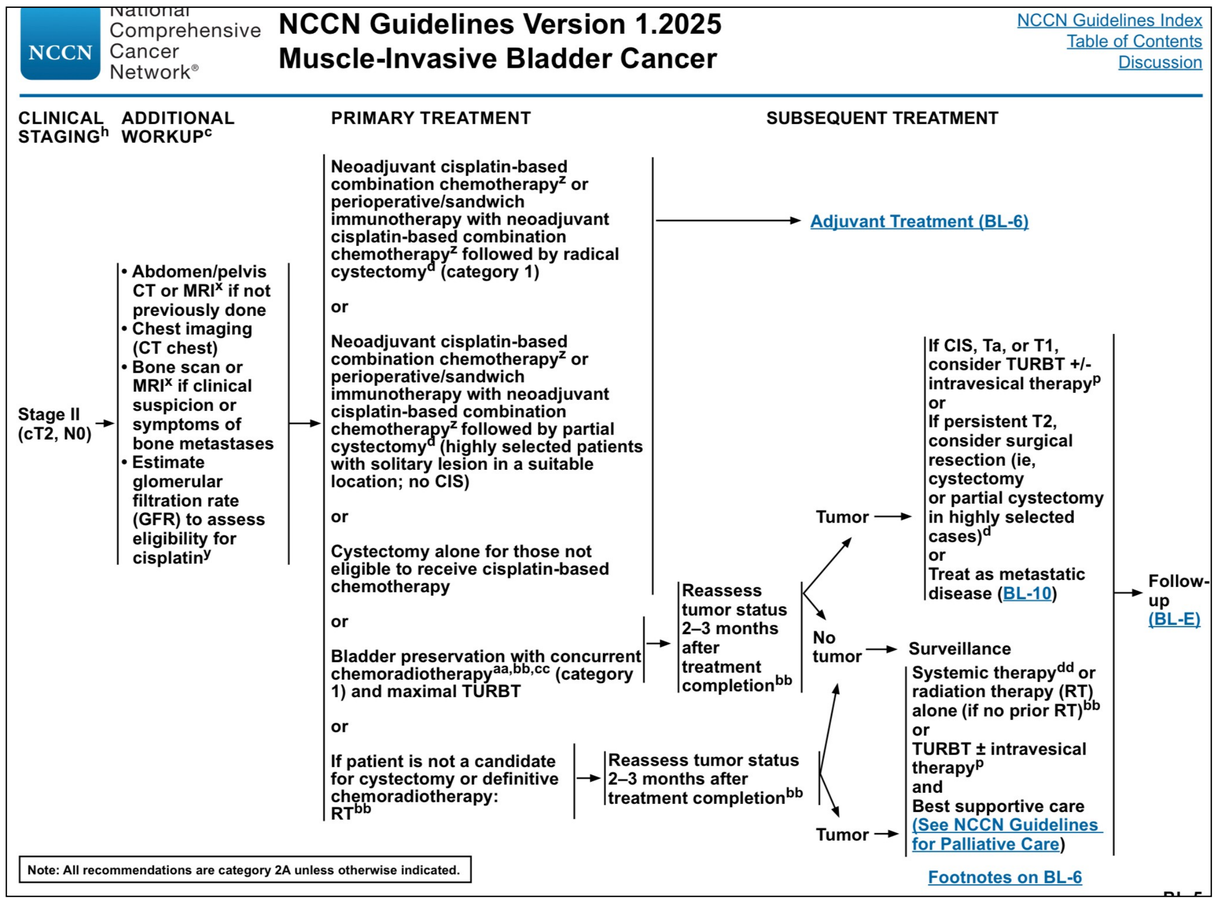
Discussion



Note: All recommendations are category 2A unless otherwise indicated.

Footnotes on BL-6

NCCN Guidelines Version 1.2025
Muscle-Invasive Bladder Cancer

NCCN Guidelines Index
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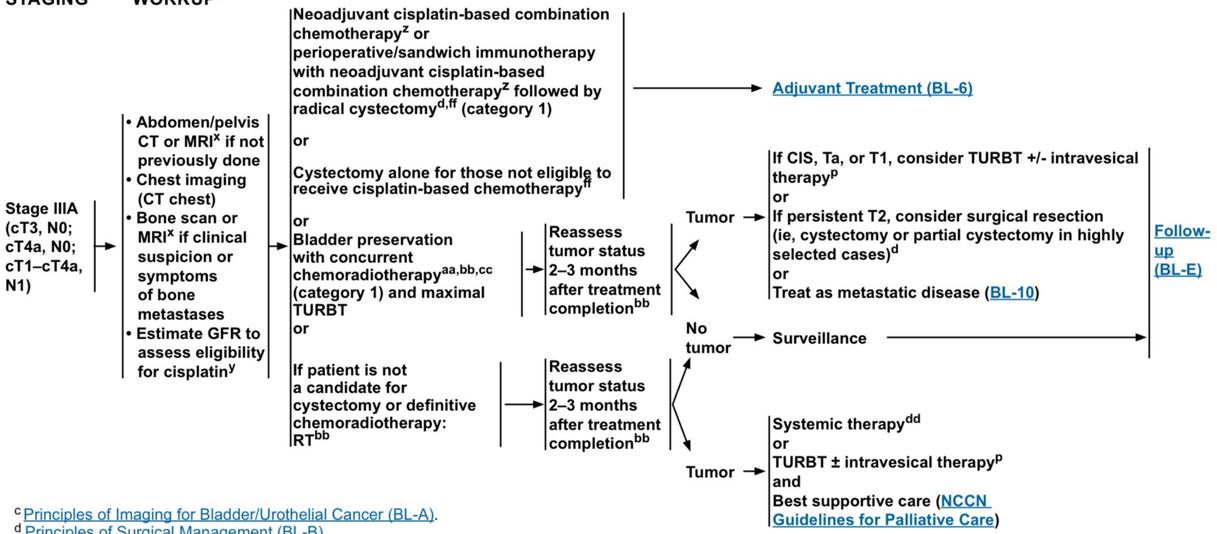


[c] Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
[d] Principles of Surgical Management (BL-B).
[h] The modifier "c" refers to clinical staging based on bimanual EUA, endoscopic surgery (biopsy or TUR), and imaging studies. The modifier "p" refers to pathologic staging based on cystectomy and lymph node dissection.
[p] Principles of Instillation Therapy (BL-F).
[x] Consider FDG-PET/CT scan (skull base to mid-thigh) (category 2B).
[y] For patients with borderline GFR, consider timed urine collection, which may more accurately determine eligibility for cisplatin.
[z] Principles of Systemic Therapy (BL-G 1 of 7).
[aa] Principles of Systemic Therapy (BL-G 5 of 7).
[bb] Principles of Radiation Management of Invasive Disease (BL-H).
[cc] Optimal candidates for bladder preservation with chemoradiotherapy include patients with tumors that present without moderate/severe hydronephrosis, are without concurrent extensive or multifocal CIS, and are <6 cm. Ideally, tumors should allow a visually complete or maximally debulking TURBT. See Principles of Radiation Management of Invasive Disease (BL-H).
[dd] Principles of Systemic Therapy (BL-G 2 of 7).
[ff] Patients with cN1 disease have better outcomes if they are given neoadjuvant chemotherapy and have a response.

Note: All recommendations are category 2A unless otherwise indicated.

Recurrent or Persistent Disease (BL-11)

PRINCIPLES OF SYSTEMIC THERAPY

Neoadjuvant Chemotherapy (preferred for bladder)	Perioperative/Sandwich Therapy
Preferred regimen • DDMVAC (dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin) with growth factor support for 3–6 cycles[1,2] **Useful in certain circumstances** • Gemcitabine and cisplatin for 4 cycles[3,4]	**Preferred regimen** • Gemcitabine + cisplatin + durvalumab prior to cystectomy, then durvalumab after cystectomy[5] (for bladder cancer only) (category 1)

Adjuvant Therapy	
No previous platinum-based neoadjuvant therapy (pT3, pT4a, pN+)	**Previous platinum-based neoadjuvant therapy (ypT2–ypT4a or ypN+)**
Preferred regimen • DDMVAC with growth factor support for 3–6 cycles[1,2] **Other recommended regimens** • Gemcitabine and cisplatin for 4 cycles[3,4] • Nivolumab[6] • Pembrolizumab[7]	**Other recommended regimen** • Nivolumab[6] • Pembrolizumab[7]

- For patients who are not candidates for cisplatin, there are no data to support a recommendation for perioperative chemotherapy.
- Randomized trials and meta-analyses show a survival benefit for cisplatin-based neoadjuvant chemotherapy (3 or 4 cycles) for MIBC.[1,8,9]
- Meta-analysis suggests overall survival benefit with adjuvant cisplatin-based chemotherapy for pathologic T3, T4 or N+ disease at cystectomy, if it was not given as neoadjuvant.[9]
- Neoadjuvant chemotherapy is preferred over adjuvant-based chemotherapy on a higher level of evidence data.
- DDMVAC is preferred over standard MVAC based on category 1 evidence for metastatic disease showing DDMVAC to be better tolerated and more effective than conventional MVAC in advanced disease.[2,10] Based on these data, the traditional dose and schedule for MVAC is no longer recommended.
- Perioperative gemcitabine and cisplatin is a reasonable alternative to DDMVAC based on category 1 evidence for metastatic disease showing equivalence to conventional MVAC in the setting of advanced disease.[4,11]
- For gemcitabine/cisplatin, a 21-day cycle is preferred. Better dose adherence may be achieved with fewer delays in dosing using the 21-day schedule.[12]
- Neoadjuvant chemotherapy is preferred for patients with UTUC, particularly for higher stage and/or grade tumors or concerning radiographic findings, as renal function will decline after nephroureterectomy and may preclude adjuvant therapy.
  - Multicenter data support the use of neoadjuvant, split-dose cisplatin-based chemotherapy (gemcitabine and cisplatin) for patients with high-grade UTUC.[13] Staging for UTUC is less precise than for bladder cancers and understaging is common, necessitating discussion on the risk of under- versus over-treatment.
  - Adjuvant therapy should be considered if neoadjuvant therapy was not given for UTUC.[14]
- Carboplatin should not be substituted for cisplatin in the perioperative bladder cancer setting.
  - For patients with borderline renal function or minimal dysfunction, a split-dose administration of cisplatin may be considered (such as 35 mg/m^2 on days 1 and 2 or days 1 and 8) (category 2B). While safer, the relative efficacy of the cisplatin-containing combination administered with such modifications remains undefined.
- For patients with borderline renal function, estimate GFR to assess eligibility for cisplatin. Consider timed urine collection, which may more accurately determine eligibility for cisplatin.
- Nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab.

Continued

References

Note: All recommendations are category 2A unless otherwise indicated.

Adjuvant Therapy

- The advantage of adjuvant, as opposed to neoadjuvant, chemotherapy is that pathologic staging allows for a more accurate selection of patients.
- Adjuvant chemotherapy has been studied in two major clinical settings: (1) after bladder-sparing chemoradiation and (2) after radical cystectomy.
- The place of adjuvant chemotherapy after cystectomy has been studied more thoroughly, but again, the results are not clear.
- Investigators generally agree that in the face of positive nodes and even with negative nodes and high pathologic stage of the primary tumor, adjuvant chemotherapy is likely to be important in improving survival.

- There are five randomized trials using adjuvant chemotherapy.
- Three studies found no difference between adjuvant chemotherapy and cystectomy alone, but all three were f lawed in design or accrual.
- Two of the five studies showed a survival benefit for cystectomy and adjuvant chemotherapy over cystectomy alone, but both are subject to criticism for both method considerations and small accrual

ELSEVIER

The Journal of Urology

Volume 148, Issue 2, Part 1, August 1992, Pages 302-306

Advanced Bladder Cancer (Stages pT3b, pT4a, pN1 and pN2): Improved Survival after Radical Cystectomy and 3 Adjuvant Cycles of Chemotherapy. Results of a Controlled Prospective Study

M. Stöckle, W. Meyenburg, S. Wellek, G. Voges, U. Gertenbach, J.W. Thüroff, Ch. Huber, R. Hohenfellner

ELSEVIER

The Journal of Urology

Volume 145, Issue 3, March 1991, Pages 459-464

Original Articles

The Role of Adjuvant Chemotherapy Following Cystectomy for Invasive Bladder Cancer: A Prospective Comparative Trial

Donald G. Skinner, John R. Daniels, Christy A. Russell, Gary Lieskovsky, Stuart D. Boyd, Peter Nichols, William Kern, Joanne Sakamoto, Mark Krailo, Susan Groshen

ELSEVIER

The Journal of Urology

Volume 152, Issue 1, July 1994, Pages 81-84

Adjuvant Cisplatin Chemotherapy Following Cystectomy for Bladder Cancer: Results of a Prospective Randomized Trial

Urs E. Studer, Marisa Bacchi, Cédric Biedermann, Peter Jaeger, Rainer Kraft, Luca Mazzucchelli, Regula Markwalder, Edgar Senn, Roland W. Sonntag

Adjuvant chemotherapy in advanced bladder cancer. Italian Uro-Oncologic Cooperative Group.

Bono AV [1], Benvenuti C , Reali L , Pozzi E , Gibba A , Cosciani-Cunico S , Comuzzi U , Anselmo G

Author information

Progress in Clinical and Biological Research, 01 Jan 1989, 303:533-540

PMID: 2675010

No Access | Journal of Urology | Clinical Urology: Original Article | 1 Feb 1996

A Randomized Trial of Radical Cystectomy Versus Radical Cystectomy Plus Cisplatin, Vinblastine and Methotrexate Chemotherapy for Muscle Invasive Bladder Cancer

Fuad Freiha, Jeffrey Reese, and Frank M. Torti

View All Author Information

https://doi.org/10.1016/S0022-5347(01)66430-9

- In a follow-up study by Stockle et al. an analysis of 166 patients, including the 49 initially randomized patients, a difference was noted in the 80 patients who received adjuvant chemotherapy compared with 86 patients who underwent cystectomy alone.
- The extent of nodal involvement proved important, and when patients were stratified by the number of nodes involved, adjuvant chemotherapy was most effective in patients with N1 disease.
- This multivariate analysis revealed a significant decrease in the risk of tumor recurrence (p = 0.0007, 2-sided) after adjuvant chemotherapy.
- The number of lymph nodes involved was also of prognostic significance (p = 0.0028, 1-sided).
- The results indicate that the survival time after radical cystectomy can be prolonged considerably by adjuvant polychemotherapy in cases of locally advanced bladder carcinoma.

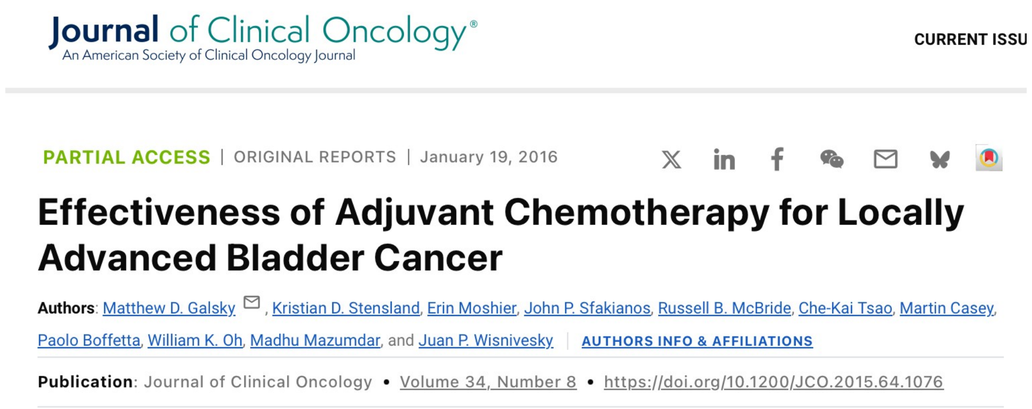
ELSEVIER

The Journal of Urology
Volume 148, Issue 2, Part 1, August 1992, Pages 302-306

Advanced Bladder Cancer (Stages pT3b, pT4a, pN1 and pN2): Improved Survival after Radical Cystectomy and 3 Adjuvant Cycles of Chemotherapy. Results of a Controlled Prospective Study

M. Stöckle, W. Meyenburg, S. Wellek, G. Voges, U. Gertenbach, J.W. Thüroff, Ch. Huber, R. Hohenfellner

- In a retrospective observational study of comparative effectiveness between postcystectomy adjuvant chemotherapy and observation in patients with pathologic T3 to T4 or node-positive bladder cancer using the National Cancer Database, 5653 patients were included, and 23% had adjuvant chemotherapy.
- Adjuvant chemotherapy was associated with longer OS (HR, 0.7; 95% CI, 0.64–0.76).
- The correlation between adjuvant chemotherapy and longer OS was consistent in subset analyses, suggesting that adjuvant chemotherapy should be considered in patients with pT3/4 and/or node-positive disease if they had not received neoadjuvant chemotherapy.



PRINCIPLES OF SYSTEMIC THERAPY

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Perioperative/Sandwich Therapy
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  - For patients with borderline renal function or minimal dysfunction, a split-dose administration of cisplatin may be considered (such as 35 mg/m^2 on days 1 and 2 or days 1 and 8) (category 2B). While safer, the relative efficacy of the cisplatin-containing combination administered with such modifications remains undefined.
- For patients with borderline renal function, estimate GFR to assess eligibility for cisplatin. Consider timed urine collection, which may more accurately determine eligibility for cisplatin.
- Nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab.

Continued

References

Note: All recommendations are category 2A unless otherwise indicated.

Metastatic Bladder Cancer

- Compared with other solid-tumor malignancies, UC is chemosensitive.
- In phase II clinical trials, radiographic response rates may be as high as 70% to 80%, and in phase III clinical trials, response rates are often on the order of 50%.
- Moreover, a small but substantial minority of responding patients manifest a CR, and among these patients, some long-term, durable responses are observed.
- Overall, however, the duration of response in UC is short, with a median of 4 months to 6 months, and therefore, the impact of chemotherapy on survival has been disappointing in metastatic disease.

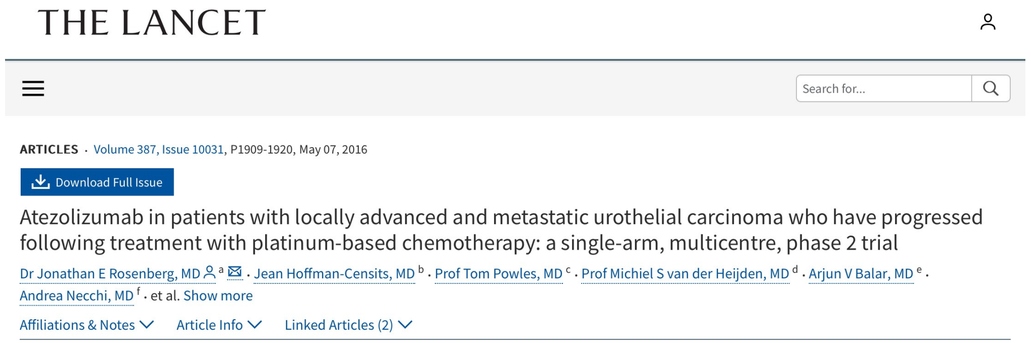
Cisplatin-Based Combination Chemotherapy

- The standard chemotherapy regimen for advanced bladder cancer for more than a decade was MVAC.
- MVAC is administered in 28-day cycles, with starting doses of methotrexate 30 mg/m2 (days 1, 15, and 22), vinblastine 3 mg/m2 (days 2, 15, and 22), doxorubicin 30 mg/m2 (day 2), and cisplatin 70 mg/m2 (day 2).
- The MVAC regimen has superior activity to cisplatin alone and to other cisplatin-containing regimens.
- Toxic effects of MVAC include neutropenia, anemia, thrombocytopenia, stomatitis, nausea, and fatigue. The rate of chemotherapy- induced fatality among patients with metastatic disease may be as high as 3%, most often caused by neutropen sepsis.

- In the randomized phase III EORTC protocol 30924, ddMVAC demonstrated improved response rate, PFS, and OS compared with standard MVAC in the metastatic setting.
- As a result of these studies, GC and ddMVAC are generally considered the current standard of care for metastatic bladder cancer.

Immune Checkpoint Inhibition

- Urothelial carcinomas elude immune surveillance by expression of PD-L1. The binding of PD-L1 to PD-1 on T cells inhibits T-cell activation and proliferation. Thus, the immune checkpoint mediated by PD-L1 and PD-1 is a therapeutic target in UC.
- A follow-up phase II trial evaluated atezolizumab in 310 patients with locally advanced or metastatic UC with disease progression after platinum-based chemotherapy.
- Atezolizumab was associated with a significantly higher response rate compared with historical chemotherapy control participants.
- Grade 3 to 4 treatment-related adverse events occurred in 16% of patients, with fatigue being most common.
- Grade 3 to 4 immune-mediated adverse events occurred in 5% of patients, including pneumonitis, elevated transaminases, rash, and dyspnea.



- Since the approval of atezolizumab, four other immune checkpoint inhibitors have been approved by the FDA as second-line therapy for advanced urothelial cancer after platinum chemotherapy: pembrolizumab (anti–PD-1), nivolumab (anti–PD-1), durvalumab (anti–PD-L1), and avelumab (anti–PD-L1).
- Is immune checkpoint therapy better than chemotherapy?

- In an open-label, phase III study, 542 patients with platinum-pretreated UC were randomized to pembrolizumab or the investigator’s choice of single-agent chemotherapy (paclitaxel, docetaxel, or vinflunine).
- Pembrolizumab was associated with significantly longer OS (10.3 months vs 7.4 months; HR for death, 0.73; 95% CI, 0.59–0.91; P = 0.002) and fewer treatment-related adverse events.
- Atezolizumab and pembrolizumab are FDA approved as firstline therapy for patients who are not eligible to receive cisplatin.

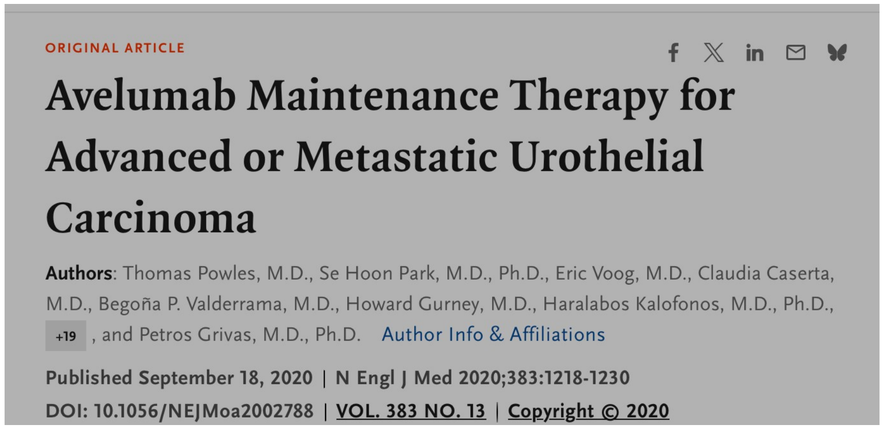
ORIGINAL ARTICLE

Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma

Authors: Joaquim Bellmunt, M.D., Ph.D., Ronald de Wit, M.D., Ph.D., David J. Vaughn, M.D., Yves Fradet, M.D., Jae-Lyun Lee, M.D., Ph.D., Lawrence Fong, M.D., Nicholas J. Vogelzang, M.D., +13 , for the KEYNOTE-045 Investigators* Author Info & Affiliations

Published March 16, 2017 | N Engl J Med 2017;376:1015-1026
DOI: 10.1056/NEJMoa1613683 | VOL. 376 NO. 11 | Copyright © 2017

- The use of avelumab as maintenance therapy after four to six cycles of platinum-based first-line chemotherapy in patients with metastatic UC was tested in randomized controlled trial of 700 patients compared with best supportive care.
- Avelumab was associated with an improvement in OS (HR for death, 0.69; 95% CI, 0.56 to 0.86; P = 0.001) as well as the secondary endpoint of PFS.
- Avelumab was approved by the FDA in 2020 as “switch maintenance” therapy after platinum-based chemotherapy.



ORIGINAL ARTICLE

Avelumab Maintenance Therapy for Advanced or Metastatic Urothelial Carcinoma

Authors: Thomas Powles, M.D., Se Hoon Park, M.D., Ph.D., Eric Voog, M.D., Claudia Caserta, M.D., Begoña P. Valderrama, M.D., Howard Gurney, M.D., Haralabos Kalofonos, M.D., Ph.D., +19 , and Petros Grivas, M.D., Ph.D. Author Info & Affiliations

Published September 18, 2020 | N Engl J Med 2020;383:1218-1230
DOI: 10.1056/NEJMoa2002788 | VOL. 383 NO. 13 | Copyright © 2020

- No treatment has surpassed platinum-based chemotherapy in improving overall survival in patients with previously untreated locally advanced or metastatic urothelial carcinoma.
- Enfortumab Vedotin (EV). EV is a novel antibody–drug conjugate (ADC), that delivers monomethyl auristatin E (MMAE), a microtubule-disrupting agent, inside cells harboring the cell surface nectin-4 receptor.
- Phase 3, global, open-label, randomized trial to compare the efficacy and safety of enfortumab vedotin and pembrolizumab with the efficacy and safety of platinum-based chemotherapy in patients with previously untreated locally advanced or metastatic urothelial carcinoma.
- Total of 886 patients underwent randomization: 442 to the enfortumab vedotin–pembrolizumab group and 444 to the chemotherapy group.
- As of August 8, 2023, the median duration of follow-up for survival was 17.2 months.
- Progression-free survival was longer in the enfortumab vedotin–pembrolizumab group than in the chemotherapy group (median, 12.5 months vs. 6.3 months; hazard ratio for disease progression or death, 0.45; 95% confidence interval [CI], 0.38 to 0.54; P<0.001), as was overall survival (median, 31.5 months vs. 16.1 months; hazard ratio for death, 0.47; 95% CI, 0.38 to 0.58; P<0.001).
- The median number of cycles was 12 (range, 1 to 46) in the enfortumab vedotin–pembrolizumab group and 6 (range, 1 to 6) in the chemotherapy group.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Enfortumab Vedotin and Pembrolizumab in Untreated Advanced Urothelial Cancer

Authors: Thomas Powles, M.D., Begoña P. Valderrama, M.D., Shilpa Gupta, M.D., Jens Bedke, M.D., Eiji Kikuchi, M.D., Ph.D., Jean Hoffman-Censits, M.D., Gopa Iyer, M.D., +17 , for the EV-302 Trial Investigators* Author Info & Affiliations

Published March 6, 2024 | **N Engl J Med 2024;390:875-888**

DOI: 10.1056/NEJMoa2312117 | **VOL. 390 NO. 10** | **Copyright © 2024**

PRINCIPLES OF SYSTEMIC THERAPY

First-Line Systemic Therapy for Locally Advanced or Metastatic Disease (Stage IV)		
Preferred regimen • Enfortumab vedotin-ejfv[15,16] and pembrolizumab (category 1)	**Other recommended regimens** • Gemcitabine and cisplatin[4] (category 1) followed by avelumab maintenance therapy (category 1)[a,17] • Gemcitabine, cisplatin, and nivolumab (category 1) followed by nivolumab maintenance therapy[18] (category 1) • DDMVAC with growth factor support[2,10] (category 1) followed by avelumab maintenance therapy (category 1)[a,17]	**Useful in certain circumstances (cisplatin-ineligible)** • Gemcitabine and carboplatin[19] followed by avelumab maintenance therapy (category 1)[a,17] • Pembrolizumab (for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for any platinum-containing chemotherapy)[20] • Atezolizumab[21] (only for patients whose tumors express PD-L1[b] or who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression) (category 2B)

- Atezolizumab and hyaluronidase-tqjs subcutaneous injection may be substituted for IV atezolizumab. Atezolizumab and hyaluronidase-tqjs has different dosing and administration instructions compared to atezolizumab for IV infusion.
- Nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab.

[a] Maintenance therapy with avelumab only if there is no progression on first-line platinum-containing chemotherapy.
[b] Atezolizumab: SP142 assay, PD-L1–stained tumor-infiltrating immune cells covering ≥5% of the tumor area.

Note: All recommendations are category 2A unless otherwise indicated.

Continued
References

Thank you

Next class

- Radical cystectomy
- Partial radical cystectomy
- Types of Urinary Diversion
- Complications of Cystectomy and Urinary Diversion
- Selective Bladder-Preserving Approaches
- Comparison of Treatment Outcomes of Contemporary Cystectomy Series with Contemporary Selective Bladder-Preserving Series
- Bladder-Preservation Treatments with Less Than Trimodality Therapy

CANCERS OF THE RENAL PELVIS AND URETER

- The majority of tumors of the upper urinary collecting system are UC.
- Men develop UTUC two to three times more often than women, with the peak age of development of these tumors in the seventh and eighth decades of life.188
- Women, however, are more likely than men to have a more advanced and higher grade tumor at nephroureterectomy.220
- Fewer than 3000 cases of upper tract malignancies are diagnosed annually in the United States.

- Gross hematuria is the presenting symptom in 75% to 95% of all patients who present with tumors of the renal pelvis and ureter.
- Hematuria may be accompanied by colicky flank pain if the tumor or blood clots cause obstruction of the upper urinary tract.
- Patients often describe the passage of vermiform clots, which are unusual in bleeding from a lower tract source.
- Hydronephrosis may also be a presenting sign and is a risk factor for invasive disease because high-grade invasive tumors may cause ureteral obstruction.
- Urinary cytology is an important part of the workup for an upper tract tumor. Voided urine cytology has only 10% to 40% sensitivity in the detection of low-grade UC lesions

- Historically, intravenous urography was the mainstay of a radiographic evaluation of upper tract tumors, but CT urography has become the standard of care (Fig. 44.6).
- MRI urography may also be useful in patients when sensitivity to iodinated contrast prevents the use of that agent.

Results Among 406 randomized eligible patients (median age, 66 years; 84.7% men), 383 completed the trial. In the intention-to-treat analysis, 67 of 201 patients (4-year estimate, 35%) in the gemcitabine group and 91 of 205 patients (4-year estimate, 47%) in the saline group had cancer recurrence within 4.0 years (hazard ratio, 0.66; 95% CI, 0.48-0.90; *P*<.001 by 1-sided log-rank test for time to recurrence). Among the 215 patients with low-grade non–muscle-invasive urothelial cancer who underwent TURBT and drug instillation, 34 of 102 patients (4-year estimate, 34%) in the gemcitabine group and 59 of 113 patients (4-year estimate, 54%) in the saline group had cancer recurrence (hazard ratio, 0.53; 95% CI, 0.35-0.81; *P* = .001 by 1-sided log-rank test for time to recurrence). Fifteen patients had tumors that progressed to muscle invasion (5 in the gemcitabine group and 10 in the saline group; *P* = .22 by 1-sided log-rank test) and 42 died of any cause (17 in the gemcitabine group and 25 in the saline group; *P* = .12 by 1-sided log-rank test). There were no grade 4 or 5 adverse events and no significant differences in adverse events of grade 3 or lower.

Conclusions and Relevance Among patients with suspected low-grade non–muscle-invasive urothelial cancer, immediate postresection intravesical instillation of gemcitabine, compared with instillation of saline, significantly reduced the risk of recurrence over a median of 4.0 years. These findings support using this therapy, but further research is needed to compare gemcitabine with other intravesical agents.

- A meta-analysis of 11 completed randomized trials of neoadjuvant chemotherapy for MIBC (3005 patients) demonstrated a 5% OS benefit at 5 years (HR, 0.86; 95% confidence interval [CI], 0.77–0.95; P = 0.003), supporting the role for platinum-based combination neoadjuvant chemotherapy.