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NCCN Guidelines® Insights Bladder Cancer, Version 2.2016 Featured Updates to the NCCN Guidelines

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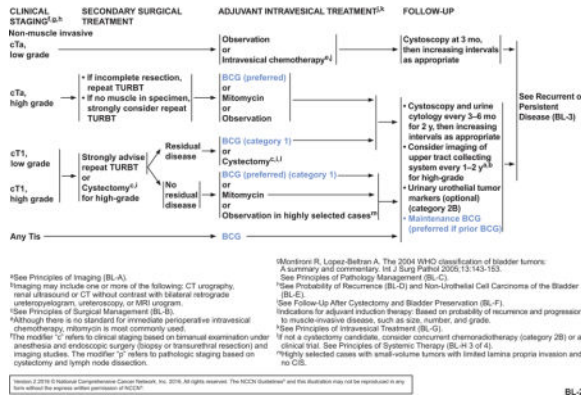
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Abstract

These NCCN Guidelines Insights discuss the major recent updates to the NCCN Guidelines for Bladder Cancer based on the review of the evidence in conjunction with the expert opinion of the panel. Recent updates include (1) refining the recommendation of intravesical bacillus Calmette-Guérin, (2) strengthening the recommendations for perioperative systemic chemotherapy, and (3) incorporating immunotherapy into second-line therapy for locally advanced or metastatic disease. These NCCN Guidelines Insights further discuss factors that affect integration of these recommendations into clinical practice.

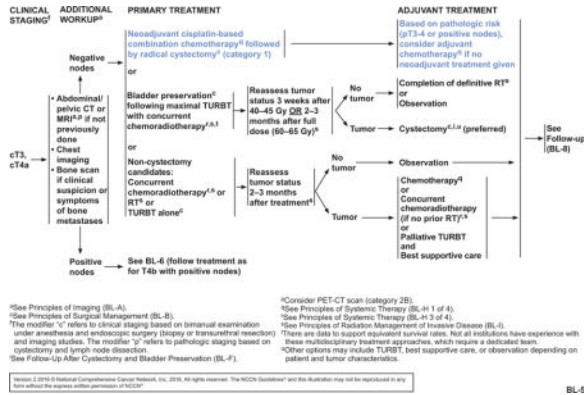


Overview

An estimated 76,960 new cases (58,950 men and 18,010 women) of urinary bladder cancer will be diagnosed in the United States in 2016, with approximately 16,390 deaths (11,820 men and 4,570 women) occurring during this same period.¹ Bladder cancer, the fifth most common cancer in the United States, is 4 times more prevalent in men than in women. Bladder cancers are rarely diagnosed in individuals younger than 40 years. Given that the median age at diagnosis is 65 years, medical comorbidities are a frequent consideration in patient management. Management of bladder cancer is based on the pathologic findings of the biopsy specimen, with attention to histology, grade, and depth of invasion. These factors are used to estimate the probability of recurrence and progression to a more advanced stage.

Transurethral resection of the bladder tumor (TURBT) with examination under anesthesia is the initial treatment for bladder cancer. The goal of TURBT is to correctly identify the clinical stage and grade of disease while completely resecting all visible tumor; therefore, an adequate sample that includes bladder muscle (ie, muscularis propria) must be in the resection specimen. For non-muscle-invasive tumors, intravesical therapy or radical cystectomy may be recommended based on the estimated probability of recurrence and progression to a more advanced stage. In patients with muscle-invasive tumors, treatment after initial TURBT is required. Different treatment modalities may be used, including radical cystectomy with or without neoadjuvant or adjuvant therapy, partial cystectomy, bladder-preserving approaches, and systemic therapy for advanced disease. Clinical trials investigating new treatments and further evidence to support current recommendations are reflected in the update of these guidelines. To view the most recent and complete version of these guidelines, visit NCCN.org.

response, including neutrophils, monocytes and macrophages, T cells, and natural killer (NK) cells. This causes patients to experience flu-like symptoms that may last 48 to 72 hours.⁸ Installation of BCG into the bladder also mimics a urinary tract infection and may produce intense local discomfort. The side effects of treatment have translated to patient refusal of BCG therapy. Local dysuria has been reported in 60% of patients in clinical trials.⁸ Symptom management with single-dose, short-term quinolones and/or anticholinergics have been reported to reduce adverse events.^{9,10} A reduced (one-third) dose of BCG has been evaluated for the possible reduction of side effects. In a phase III study, 1,316 patients with intermediate- or high-risk Ta, T1 papillary carcinoma of the bladder were randomized to receive either reduced- or full-dose BCG for either 1 or 3 years of maintenance.¹¹ Among all 4 groups, the percentage of patients with 1 or more side effect was similar ($P=.41$). Although the one-third dose of BCG was effective, side effects were not reduced. Conversely, other publications suggest that the one-third dose may reduce side effects.¹²⁻¹⁴ Full-dose BCG is recommended by the panel until more data are available to evaluate the low-dose BCG regimen. However, dose reduction may be used if there are substantial local symptoms during maintenance.



Timing and duration of maintenance BCG remain a subject of debate. BCG therapy is commonly given once a week for 6 weeks, followed by a rest period of 4 to 6 weeks, with a full re-evaluation at week 12 (ie, 3 months) after the start of therapy.¹⁵ There is less agreement for the optimal schedule of maintenance BCG. The controversy over the effectiveness of BCG maintenance reflects the wide array of schedules and conflicting reports of efficacy. Quarterly and monthly installations and 3- and 6-week schedules have been evaluated. To date, the strongest data support the 3-week BCG regimen used in the SWOG trial, which demonstrated reduced disease progression and metastasis.¹⁶ The 3-week timing of BCG has shown improved outcomes compared with epirubicin¹⁷ or isoniazid.¹⁸ Most patients receive maintenance BCG for 1 to 3 years. In an evaluation of randomized controlled trials and meta-analyses, limited evidence was found for 1 year of BCG maintenance.¹⁹ Conversely, a study of 1,355 patients with a median follow-up of 7.1 years found no benefit with 3 years of maintenance BCG compared with 1 year for intermediate-risk patients.²⁰ In high-risk patients, 3-year maintenance BCG reduced recurrence compared with 1-year maintenance, but did not impact progression or survival. These data suggest that 1 year of maintenance may be suitable for patients at intermediate risk. It should also be noted that duration of treatment may be limited by toxicity and patient refusal to continue.

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BCG is not recommended for low-grade Ta tumors due to the low risk of disease progression. The NCCN Guidelines for Bladder Cancer generally manage Tis, high-grade Ta, or T1 tumors with intravesical BCG therapy or cystectomy (see BL-2, page 1215). Primary Tis is a high-grade lesion that is managed with resection followed by intravesical therapy with BCG. Patients with high-grade Ta tumors may be treated with intravesical BCG (preferred) or mitomycin C. A repeat TURBT is strongly advised for patients with T1 disease. As long as no muscle-invasive disease is found after the second resection, intravesical therapy with BCG (preferred; category 1) or mitomycin C (category 2A) is recommended. Observation may be reasonable in highly select cases where small-volume tumors had limited lamina propria invasion and no Tis.^{21,22} If residual disease is found, treatment should consist of BCG (category 1) or cystectomy (category 2A). Within T1 disease, a particularly high-risk stratum can be identified: multifocal lesions, tumors associated with carcinoma in situ or lymphovascular invasion, micropapillary tumors, or lesions that recur after BCG treatment. There are data suggesting that early cystectomy may be preferred if residual disease is found because of the high risk for progression to a more advanced stage.²³

PRINCIPLES OF SYSTEMIC THERAPY
First-line chemotherapy for locally advanced or metastatic disease

	Standard regimens	Alternate regimens for select patients
Cisplatin eligible	<ul style="list-style-type: none"> • Gemcitabine and cisplatin⁴ (category 1) • DDWVAC with growth factor support (category 1)^{2,3} 	
Cisplatin ineligible with poor kidney function or poor PS	<ul style="list-style-type: none"> • Gemcitabine and carboplatin¹¹ 	<ul style="list-style-type: none"> • Gemcitabine¹² • Gemcitabine and paclitaxel¹³
Cisplatin ineligible due to hearing/ neuropathy but with good kidney function, and good PS		<ul style="list-style-type: none"> • Ifosfamide, docosubicin, and gemcitabine¹⁴

• The presence of both visceral metastases and ECOG performance score ≥ 2 strongly predict poor outcome with chemotherapy. Patients without these adverse prognostic factors have the greatest benefit from chemotherapy.
 • For most patients, the risks of adding paclitaxel to gemcitabine and cisplatin outweigh the limited benefit seen in the randomized trial.¹³
 • A substantial proportion of patients cannot receive cisplatin-based chemotherapy due to renal impairment or other comorbidities.
 • Participation in clinical trials of new or more tolerable therapy is recommended.

Second-line systemic therapy for locally advanced or metastatic disease

• No standard therapy exists in this setting; thus, participation in clinical trials of new agents is recommended.
 • The standard and alternate options are listed below.

Standard regimens	Alternate regimens for select patients
<ul style="list-style-type: none"> • Ifosfamide¹⁵ • Paclitaxel or docetaxel¹⁷ • Gemcitabine¹² • Farnesitaxel¹⁸ 	<ul style="list-style-type: none"> • Nab-paclitaxel¹⁶ • Ifosfamide¹⁵ • Methotrexate • Ifosfamide, docosubicin, and gemcitabine¹⁴ • Gemcitabine and paclitaxel¹³ • Gemcitabine and cisplatin⁴ • DDWVAC^{2,3}

Continued on BL-H 3 of 4
References on BL-H 4 of 4

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BL-H
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After the initial intravesical treatment and 12-week evaluation, patients with persistent cTa, cT1, or Tis disease tumors can be given a second induction course of BCG induction therapy (see BL-3, page 1216); no more than 2 consecutive induction courses should be given. If a second course of BCG is given, TURBT is performed to determine the presence of residual disease at the second 12-week follow-up. If no residual disease is found, maintenance BCG is recommended and preferred for patients who received prior BCG. If residual disease is seen after TURBT, patients with persistent high-grade cT1 tumors are recommended to proceed to cystectomy. Patients with persistent Tis or cTa disease after TURBT may be treated with intravesical therapy using a different intravesical agent or cystectomy. For patients with disease that does not respond to BCG or that shows an incomplete response, subsequent management options include cystectomy, change in intravesical agent, and participation in a clinical trial. Although a few NCCN Member Institutions do not routinely administer maintenance BCG, panel consensus is to recommend maintenance BCG if prior BCG was given. This recommendation is based on findings that an induction course of BCG intravesical therapy followed by a maintenance regimen produced better outcomes than intravesical chemotherapy.^{2,3,16,24–26}

Perioperative Chemotherapy

One of the most noteworthy issues in the treatment of bladder cancer is the optimal use of perioperative chemotherapy for muscle-invasive disease. Data support the role of neoadjuvant chemotherapy before cystectomy for T2, T3, and T4a lesions.²⁷⁻³² In a SWOG randomized trial of 307 patients with muscle-invasive disease that compared radical cystectomy alone versus 3 cycles of neoadjuvant methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) followed by radical cystectomy, neoadjuvant chemotherapy increased median survival (77 vs 46 months; $P=.06$) and lowered the rate of residual disease (15% vs 38%; $P<.001$) with no apparent increase in treatment-related morbidity or mortality.²⁷ Another trial randomized 196 patients with invasive bladder cancer to 2 cycles of neoadjuvant MVAC before radical cystectomy or cystectomy only.³³ Neoadjuvant chemotherapy resulted in more patients achieving pT0 than cystectomy alone (34% vs 9%; $P<.01$). Overall survival (OS) favored the neoadjuvant group, although it did not reach statistical significance.³³ In a meta-analysis of 11 trials involving 3,005 patients, cisplatin-based neoadjuvant chemotherapy was associated with improved 5-year OS and disease-free survival (DFS) (5% and 9% absolute improvement, respectively).³⁴

Since the neoadjuvant trial with MVAC, the use of dose-dense MVAC (ddMVAC) with growth factor support in the metastatic setting has been shown to have good comparable tolerance, with an increased complete response rate compared with standard dosing of MVAC (11% vs 25%; 2-sided $P=.006$).³⁵ Based on these findings, ddMVAC has also been investigated in the neoadjuvant setting. In a multicenter prospective phase II trial, patients with cT2 to cT4a tumor staging and N0 or N1 muscle-invasive bladder cancer ($n=44$) were given 3 cycles of ddMVAC with pegfilgrastim followed by radical cystectomy and lymph node dissection.³⁶ ddMVAC was anticipated to have a safer profile, a shorter time to surgery, and a similar pathologic complete response rate compared with historical control data for neoadjuvant MVAC chemotherapy given in previous studies. Patients receiving ddMVAC had no grade 3 or 4 renal toxicities and no toxicity-related deaths. Grade 1 or 2 treatment-related toxicities were seen in 82% of patients. The median time to cystectomy was 9.7 weeks from the start of chemotherapy.³⁶ A separate single-arm phase II study also reported pathologic downstaging in 49% of patients receiving neoadjuvant ddMVAC with a similar safety profile.³⁷ An additional neoadjuvant clinical trial of ddMVAC with bevacizumab reported 5-year survival outcomes of 63% and 64% (OS and disease-specific survival, respectively; median follow-up, 49 months), with pT0N0 and less than or equal to pT1N0 downstaging rates of 38% and 53%, respectively.³⁸ Bevacizumab had no definitive impact on overall outcomes.

Despite evidence that neoadjuvant chemotherapy targets micrometastases and improves patient outcomes, clinical practice has been slow to incorporate this combination therapy. A survey of physicians reported the underuse of neoadjuvant chemotherapy by 30% to 57%.³⁹ Common physician concerns included patient age or presence of comorbidities, delay of definitive treatment, and a presumed lack of evidence to support neoadjuvant chemotherapy.^{39,40} Although the NCCN Bladder Cancer Panel recognizes the potential for increased morbidity with chemotherapy and the potential delay in definitive treatment, the substantial benefits outweigh the risks when used appropriately. In addition to the benefit

from early reduction of micrometastases, there may be improved drug delivery and patient tolerance in the preoperative setting.

Data are less clear regarding the role of adjuvant systemic chemotherapy in invasive bladder cancer. Studies have shown that adjuvant chemotherapy may delay recurrences and improve OS,^{41–43} but no randomized comparisons of adequate sample size have definitively shown a survival benefit, in large part due to the poor accrual.⁴⁴ Clinical trials of adjuvant chemotherapy with cyclophosphamide, doxorubicin, and cisplatin (CAP); MVAC; and methotrexate, vinblastine, epirubicin, and cisplatin (MVEC) regimens have each suggested a survival advantage.^{45–47} However, methodologic issues call into question the applicability of these studies to all patients with urothelial tumors. In the MVEC trial, patients who experienced relapse in the control arm did not undergo chemotherapy, which is not typical of more contemporary series. Many trials were not randomized, raising the question of selection bias in the analysis of outcomes. A meta-analysis of 6 trials found a 25% mortality reduction with adjuvant chemotherapy, but the authors pointed out several limitations of the data and concluded that evidence is insufficient for treatment decisions.⁴⁸ Interestingly, the follow-up analysis included 3 more studies, for a total of 9 trials (N=945 patients).⁴³ A 23% risk reduction for death was observed in the updated analysis (hazard ratio [HR], 0.77; 95% CI, 0.59–0.99; *P*=.049) and improved DFS was achieved (HR, 0.66; 95% CI, 0.45–0.91; *P*=.014). Patients with nodepositive disease had an even greater DFS benefit.⁴³ A recent observational study evaluated 5,653 patients, of which 23% received adjuvant chemotherapy postcystectomy.⁴² Patients who received adjuvant chemotherapy had an improved OS (HR, 0.70; 95% CI, 0.06–0.76).⁴² Although evidence for adjuvant therapy is not as strong as for neoadjuvant therapy, the growing body of data support the administration of adjuvant chemotherapy for patients with a high risk for relapse who did not receive neoadjuvant therapy.

The NCCN Bladder Cancer Panel strengthened the recommendations for neoadjuvant chemotherapy for patients with cT2, cT3, and cT4a bladder cancer, and for adjuvant chemotherapy for patients with pT3 or pT4 disease or positive nodes (see BL-4 and BL-5, pages 1217 and 1218). Neoadjuvant chemotherapy followed by radical cystectomy is a category 1 recommendation by the panel. Patients with hearing loss or neuropathy, poor performance status, or renal insufficiency may not be eligible for cisplatin-based neoadjuvant chemotherapy. For patients with borderline renal function or minimal dysfunction, a split-dose administration of cisplatin may be considered (category 2B). Although split-dose is a safer alternative, the relative efficacy remains undefined. Adjuvant chemotherapy may be given to patients with high-risk pathology who did not receive neoadjuvant chemotherapy (category 2A). For highly select patients who undergo a partial cystectomy, neoadjuvant chemotherapy is a category 2A recommendation, with the option of adjuvant chemotherapy for patients who did not receive neoadjuvant chemotherapy (see BL-4, page 1217). A minimum of 3 cycles of a cisplatin-based combination, such as ddMVAC, gemcitabine plus cisplatin, or CMV (cisplatin, methotrexate, and vinblastine), may be used in patients undergoing perioperative chemotherapy. Regimen and dosing recommendations are mainly based on studies in advanced disease.^{27,32,49–51} Carboplatin has not demonstrated a survival benefit and should not be substituted for cisplatin in the perioperative setting. It should be noted that patients with tumors that are pT2 or less and

have no nodal involvement or lymphovascular invasion after cystectomy are considered to have lower risk and are not recommended to receive adjuvant chemotherapy. Data are limited to support perioperative chemotherapy for nonurothelial carcinomas; however, neoadjuvant chemotherapy may have benefit in patients with small cell carcinoma of the bladder, and is recommended by the panel for any patient with small-cell component histology with localized disease, regardless of stage.^{52–55}

Targeted Immunotherapy

Platinum-based chemotherapy has been the standard of care in patients with metastatic disease with an OS of 9 to 15 months.^{56,57} However, in patients with disease that relapses after this type of chemotherapy, the median survival is reduced to 5 to 7 months.⁵⁸ Several new agents for the treatment of metastatic urothelial carcinoma are being advanced in clinical trials, and early data suggest improved outcomes compared with standard therapies.

PD-1 and PD-L1 checkpoint inhibitors have garnered attention recently based on clinical trial data and the FDA approval of the PD-L1 inhibitor atezolizumab. Atezolizumab is approved for the treatment of locally advanced or metastatic urothelial cell carcinoma that has progressed during or after platinum-based chemotherapy or that has progressed within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy, regardless of PD-L1 expression levels. In a single-arm, multicenter, phase II trial in 310 patients with metastatic urothelial carcinoma that progressed after treatment with platinum-based chemotherapy, data showed a significantly improved objective response rate compared with historical controls (15% vs 10%; $P=.0058$).⁵⁹ Notably and consistent to observation of checkpoint inhibitors in other cancer types, responses tended to be durable, with ongoing responses recorded in 38 of 45 responders (84%) with a median follow-up of 11.7 months. Although a similar response rate was seen regardless of PD-L1 status of tumor cells, a greater response was associated with increased PD-L1 expression status on infiltrating immune cells in the tumor microenvironment. Grade 3 or 4 treatment-related or immune-mediated adverse events occurred in 16% and 5% of patients, respectively. Furthermore, there were no treatment-related deaths in this trial, suggesting good tolerability. Atezolizumab marks the first immunotherapy to be approved for patients with advanced urothelial carcinoma, a setting that has had a dearth of new therapies.

Durvalumab and avelumab are 2 other PD-L1 inhibitors in clinical trials to evaluate their activity in the treatment of bladder cancer. Early results from a phase I/II multicenter study of 61 patients has led to FDA breakthrough therapy designation of durvalumab for patients with PD-L1–positive inoperable or metastatic urothelial bladder cancer with a tumor that has progressed during or after one standard platinum-based regimen. In this study, 46.4% of patients who were PD-L1-positive experienced a response to treatment; no response was seen in those who were PD-L1-negative.⁶⁰ Median duration of response for 12 of the 13 patients was not yet reached at the time of publication (range, 4.1–49.3 weeks). Results from the phase Ib trial for patients with platinum-refractory disease or who are ineligible for cisplatin-based chemotherapy demonstrated an overall response rate (ORR) of 18.2% that consisted of 2 complete responses and 6 partial responses after treatment with avelumab.⁶¹ A higher progression-free survival was seen in patients with positive PD-L1 tumor cells

versus patients that did not express PD-L1 (58.3% vs 16.6% at 24 weeks), although some patients who were PD-L1-negative did experience a response to treatment.

Nivolumab and pembrolizumab are antibodies directed towards PD-1. Nivolumab is indicated for the treatment of several advanced and metastatic cancers and has been granted FDA breakthrough status for the treatment of advanced bladder cancer. In a phase I/II trial in patients with locally advanced or metastatic urothelial carcinoma that progressed after treatment with at least one platinum-containing regimen, early data showed an objective response rate of 24% (95% CI, 15.3%–35.4%) that was unaffected by PD-1 tumor status.⁶² Of the 78 patients enrolled in the study, 2 experienced grade 5 treatment-related adverse events, and grade 3 or 4 treatment-related adverse events were reported in 22% of patients.⁶² Pembrolizumab has been evaluated as second-line therapy for patients with bladder cancer who previously received platinum-based therapy and who subsequently experienced disease progression or metastasis.^{63,64} The ORR was 25% in this trial, with 7 of the 22 patients reporting a complete or partial response.⁶⁵ Grade 3 to 4 adverse events occurred in 15% of patients.⁶⁵

Emerging data are encouraging for the effectiveness of checkpoint inhibitors in the treatment of urothelial carcinoma. Cancers with higher rates of somatic mutations have been shown to respond better to checkpoint inhibitors.^{66–71} Data from The Cancer Genome Atlas rank bladder cancer as the third highest mutated cancer,^{72,73} suggesting that checkpoint inhibitors may have a substantial impact as a treatment option for this cancer. The value of checkpoint inhibitors is reflected in the unanimous decision by the NCCN panel to include atezolizumab as a second-line systemic therapy for locally advanced or metastatic disease after platinum-based therapy (see BL-H 2 of 4, page 1219).

Conclusions

The advancement of treatment options for bladder cancer is illustrated by the array of treatment modalities and clinical trials. It has been 40 years since immunotherapy was first implemented as a therapy in bladder cancer. BCG has become the backbone of treatment for high-grade, non-muscle-invasive bladder cancer. Checkpoint inhibitors have emerged as a second immunotherapy option for urothelial carcinoma. In addition, neoadjuvant and adjuvant therapies have gained wider acceptance. Experts surmise that the treatment of urothelial tumors will evolve rapidly over the next few years, with improved outcomes for patients at all stages of disease. Although advances are expected, improvement of patient outcomes will only be achieved with the universal implementation of these changes in clinical practice.

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Learning Objectives

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to NCCN Guidelines for Bladder Cancer
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Bladder Cancer

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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Posttest Questions

1. Which immunotherapy or immunotherapies is/are FDA-approved for use in patients with bladder cancer?
 1. BCG
 2. Atezolizumab
 3. Durvalumab
 4. Avelumab
 - a. 2
 - b. 1 and 2
 - c. 2 and 3
 - d. All of the above
2. Which statement about BCG is false?
 - a. Early cystectomy may be preferred to BCG in patients with high-risk T1 disease
 - b. Duration of BCG treatment may be limited by toxicity
 - c. Tis, Ta, or T1 tumors are all generally managed with intravesical BCG therapy or cystectomy
 - d. The most common timing for BCG maintenance is the 3-week schedule
3. True or False: Patients who are cisplatin-ineligible can consider carboplatin-based chemotherapy in the perioperative setting.