AUA NEWS

2017 ANNUAL MEETING HIGHLIGHTS
Bladder Cancer

Course #002IC
Chemotherapy and Immunotherapy Options for Genitourinary Malignancies

Course #017IC
AUA Guidelines 2017: Non-Muscle Invasive Bladder Cancer

Course #056IC
Difficult Cases in High Risk Bladder Cancer: An Evidence-Based Approach

Course #075IC
AUA/ASCO/ASTRO/SUO Guidelines 2017: Muscle Invasive Bladder Cancer

Course #085IC
Management of Nonmuscle Invasive Bladder Cancer: Practical Solutions for Common Problems

Plenary Session
Next Frontier: State-of-the-Art Lecture: Immunotherapy for Bladder Cancer

AUA2017 ANNUAL MEETING HIGHLIGHTS
Bladder Cancer

Supported by an independent educational grant from Merck.
2017 AUA Annual Meeting Highlights: Bladder Cancer

Method of Participation
To claim CME credit/hours of participation, the learner must read the overview of courses 002IC, 017IC, 056IC, 075IC and 085IC, complete the posttest, passing with 80% accuracy, and submit the evaluation and credit request form by visiting www.AUAnet.org/17BCHighlights.

Estimated time to complete this activity: 1.25 hours
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Target Audience
Urologists, urologists in training and non-physician providers involved in urology.

Course #002IC: Chemotherapy and Immunotherapy Options for Genitourinary Malignancies

Learning Objectives
At the conclusion of this CME activity, participants should be able to:

• Obtain familiarization with standard of care chemotherapy regimens for genitourinary malignancies
• Obtain familiarization with newer immunotherapy options in the treatment of genitourinary malignancies
• Enhance the identification and management of toxicities with relation to these agents
• Identify the survivorship issues surrounding patients on systemic treatments for genitourinary malignancies

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Disclosures: Nothing to disclose

Course #017IC: AUA Guidelines 2017: Non-Muscle Invasive Bladder Cancer

Learning Objectives
At the conclusion of this CME activity, participants should be able to:

• Analyze the latest evidence on the management of non-muscle invasive bladder cancer as outlined in the AUA guidelines
• Improve the therapeutic decision making processes by illustrating the application of these guidelines in urological practice
• Acquire in-depth knowledge on the process by which evidence is used to develop scientifically rigorous, yet actionable, guidelines

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Learning Objectives

At the conclusion of this CME activity, participants should be able to:

• Analyze the latest evidence on the management of muscle invasive bladder cancer as outlined in the AUA guidelines
• Improve the diagnostic and therapeutic decision making processes by illustrating the application of these guidelines in urological practice
• Acquire in-depth knowledge on the process by which evidence is used to develop scientifically rigorous, yet actionable, guidelines

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Course #085IC: Management of Nonmuscle Invasive Bladder Cancer: Practice Solutions for Common Problems

Learning Objectives

At the conclusion of this CME activity, participants should be able to:

- Implement the 2015 practice guidelines into the office setting
- Identify the best intravesical agent and duration of therapy for low, intermediate and high risk settings
- Identify methods to treat significant toxicities from various intravesical therapies
- Define high risk scenarios that necessitate cystectomy

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Chemotherapy and Immunotherapy Options for Genitourinary Malignancies

Costas D. Lallas, MD, FACS, Course Director; Anne E. Calvaresi, MSN, CRNP and Edouard J. Trabulsi, MD, FACS, Faculty

The new generation of management of genitourinary malignancies is marked by multidisciplinary care, interdisciplinary conferences and collaborative efforts. Long gone are the days when these patients were treated by clinicians operating out of separate silos with outcomes often determined by one person making the majority of the decisions surrounding care.

Concurrently, urologists countrywide are facing a profound workforce shortage. Although it is conceivable that office urology, including the diagnosis and behavioral or medical treatment of straightforward urological maladies, can be offloaded to primary care physicians, the treatment of patients with genitourinary malignancies should never be performed far from the input of a urologic oncologist.

Putting this all together, namely the emergence of multidisciplinary management of genitourinary malignancies and the impending workforce shortage in urology, the position of the advanced practice provider (APP) has been created, with directed formal training in urologic oncology. These physician extenders (nurse practitioners and physician assistants) may work independently to increase the bandwidth of a urologic oncologist, but make decisions ultimately dictated, either directly or indirectly, by the physician.

The usefulness of the urologic oncology APP is clearly evident in treating patients with bladder cancer. The APP must be familiar with the staging of this heterogeneous disease, in addition to treatments for the variety of disease states and their relative efficacies and potential side effects. The APP will serve as the front line clinician, conveying much of the clinical information and triaging, whatever surprises come through the door.

For superficial bladder cancer APPs are responsible for administering intravesical therapies and, in addition to the scheduling of induction as well as maintenance courses of these treatments, they must know the intricacies of each agent, especially their individual side effects and toxicities. Depending on specific physician or group practice patterns, APPs may be performing procedures, and it becomes their responsibility to diagnose a recurrence or raise the red flag of a potential progression. Finally, APPs should be able to discern the finer points of superficial bladder cancer, such as interpreting urine cytology, determining when to order upper tract imaging or deciding when to break the routine maintenance cystoscopy schedule.

The multidisciplinary management of muscle invasive or metastatic bladder cancer elucidates the value of an APP who is well trained in urologic oncology. The APP often troubleshoots difficulties with a urinary diversion, including stomal complications and catheterization of continent diversions. Additionally, the APP can easily screen a patient with a urinary diversion for metabolic or electrolyte disorders, or infection.

The fluid movement of these patients between the offices of the medical oncologist and the urologic oncologist requires a familiarity with the systemic therapies that are being administered to these patients. These therapies fall into the 2 general categories of chemotherapy and immunotherapy. The stated objectives of this course included familiarizing APPs with the commonly used agents for muscle invasive and metastatic bladder cancer.

Chemotherapy has long been used to treat advanced urothelial malignancies, with cisplatin being the most active agent and first chemotherapy drug approved for the treatment of bladder cancer. One of the first combination regimens that included cisplatin and demonstrated good efficacy against urothelial malignancies was MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin). MVAC has been described in the neoadjuvant and adjuvant settings but demonstrated a clear survival benefit in a landmark article comparing neoadjuvant MVAC to cystectomy alone, with ypT0 (complete response [CR]) patients having the best outcomes.

MVAC can be given in a standard 3 to 4 course regimen over several months or in an accelerated, dose dense regimen (DDMVAC) over 6 weeks. DDMVCAC has demonstrated response rates superior to those of standard MVAC, with a higher CR rate and median progression-free survival but little difference in median overall survival. However, MVAC and DDMVCAC have a relatively harsh toxicity profile, including grade 3-4 hematologic toxicities and mucositis, nephrotoxicity, ototoxicity, emesis and peripheral neuropathy.

Accordingly, more recently cisplatin has been administered in combination with gemcitabine with similar response rates and overall survival, but better tolerability. Still, one of the major limitations of cisplatin based chemotherapy regimens is that several patients may not be considered candidates before administration because of underlying renal insufficiency, hearing loss, neuropathy or generalized frailty. Unfortunately, alternate regimens with similar agents do not demonstrate similar efficacy.

Most urologists and their extenders are familiar with immunotherapy for bladder cancer. Bacillus Calmette-Guérin (BCG) was approved by the FDA (Food and Drug Administration) for the treatment of superficial bladder cancer in 1990 and it is still considered standard of care for noninvasive, high...
grade urothelial carcinoma of the bladder. However, despite its relative success the mechanism of BCG has not been fully elucidated.

It is generally believed to elicit an immune response much like native tuberculosis, for which BCG was first created as a potential vaccine. In addition, the relatively muted response of BCG in an immune deficient state suggests its foundation in immunotherapy. Although BCG is associated with ease of administration and tolerability, it can cause particularly toxic side effects, including dysuria, fevers, arthralgia and (thankfully rarely) BCG induced sepsis, and it should never be administered in the setting of active infection or gross hematuria.

Most of the recent excitement surrounding immunotherapy and bladder cancer lies in the introduction of checkpoint inhibitors. The astounding efficacy of this class of medications against urothelial cancer prompted a well-known and established genitourinary oncologist to state at an international meeting that he had “not seen such dramatic responses in my 30 years of treating these cancers.”

The checkpoint proteins are molecules that impede immune function (namely T-cell immunity). In a normal individual this immune regulation helps the body to recognize self and prevent autoimmunity and immune overactivity. However, malignant cells can hijack this mechanism and mimic the signals released by healthy cells. In so doing, the immune system remains inactive against the malignant cells, allowing them to grow and proliferate unregulated.

A checkpoint inhibitor takes the proverbial foot off of the brake and activates the cellular response, allowing the immune system to attack the malignant cells. Three checkpoint targets are currently the focus of investigation, namely PD-1 and CTLA-4 (on the T-cell), and PD-L1 (on the tumor cell). Atezolizumab is a monoclonal antibody, the first described PD-L1 inhibitor found to be active in bladder cancer. It received accelerated approval by the FDA for the treatment of urothelial cancer after failed platinum based chemotherapy. The basis for the FDA approval was the phase 2 IMVigor trial, which demonstrated an objective response rate of 16% in 310 patients with platinum treated inoperable, locally advanced or metastatic urothelial carcinoma. Among those patients who responded, these responses tended to be durable. Grade 3/4 toxicity was low as was the rate of discontinuation from the study. In addition to atezolizumab, several other checkpoint inhibitors against PD-1, PD-L1 and CTLA-4 are under investigation.

Interestingly, costimulatory proteins such as CD28, that activate the immune response, are also being investigated. Going along with the driving analogy, these signals are like stepping on the gas to further propel the cellular response against malignancies. One need only look at the number of checkpoint and costimulatory proteins that have been discovered to imagine the true potential of immunotherapy, considering that mitigation of inhibition and activation of stimulation (i.e. taking the foot off of the brake and stepping on the gas) can be used in combination to drive the immune response against bladder cancer (see figure). Staying abreast of these treatments is imperative to the urologic oncologist and their extenders, who will be co-managing these cases.

AUA Guidelines 2017: Non-Muscle Invasive Bladder Cancer

Chad R. Ritch, MD, MBA and Sam S. Chang, MD, MBA, Course Co-Directors

This course provided an overview of the current AUA Guideline for the Management of Non-Muscle Invasive Bladder Cancer (NMIBC), and target ed health care providers who primarily manage NMIBC as well as those urologists preparing for board certification/recertification.

The course began with a review of...
guideline methodology and described the process of data collection involved in guideline creation. To develop the NMIBC guidelines a systematic review of more than 200 NMIBC studies was undertaken by the AHRQ (Agency for Healthcare Research and Quality).²

The AHRQ group assessed these studies for risk of bias and whether they were fit for inclusion in the guideline. Strict criteria for level of evidence (A, B, C) and strengths of recommendation, as defined by the AUA, were then applied. In addition, where study data were limited the statement was graded as “clinical principle” (ie general agreement among most urologists) or “expert opinion” (general consensus among guideline panel members).

Next, key epidemiological characteristics of bladder cancer were presented, eg the fourth most common solid malignancy in men and approximately 75% of the 74,000 new cases of bladder cancer each year are NMIBC.³ Etiologic factors were described that include tobacco smoking and exposure to chemical carcinogens, and genetic mutations in tumor suppressor genes such as p53 and RB-1 were discussed as well. Staging and grading based on the most recent version of the American Joint Committee on Cancer TNM classification and the WHO/International Society of Urological Pathology grading system were presented.

The survival prognosis for patients with NMIBC (stages Ta, Tis and T1) is relatively favorable, with cancer specific survival in high grade disease ranging from approximately 70% to 85% at 10 years. The heterogeneous spectrum of NMIBC was described, specifically with respect to prognosis as defined by recurrence and progression. While some tumors are more likely to recur, others are more likely to progress despite subtle differences in stage and grade. To this end, it was emphasized throughout the course that the AUA guidelines panel decided to incorporate a risk stratification system as a part of the new algorithm for the management of NMIBC.

The AUA risk stratification was derived from data used to develop the EORTC (European Organisation for Research and Treatment of Cancer)⁴ and CUETO (Club Urológico Español de Tratamiento Oncológico) models,⁵ and expands on these tools to include the prognostic impact of bacillus Calmette-Guérin (BCG) treatment failure, as well as adverse pathological features such as the presence of lymphovascular involvement, prostatic urethral involvement and variant histology. A point of emphasis was that at each instance of occurrence or recurrence, the risk stratification tool should be applied to the patient algorithm to ensure adherence to the guidelines.

The course faculty then presented and discussed each guideline statement and supporting evidence, in depth, with relevant background data. A detailed listing of the statements and references can be found at https://www.auanet.org/guidelines/non-muscle-invasive-bladder-cancer- (aua/suo-joint-guideline-2016). The first 4 statements are essential clinical principles for documenting and diagnosing NMIBC (cystoscopy, transurethral resection and tumor description in operative/procedural notes).

Statement 5 is unique to the current guidelines as it specifically recommends that risk stratification be performed, using the AUA risk grouping of low, intermediate and high, at each occurrence/recurrence of NMIBC. The emphasis on risk stratification is to aid in a more personalized approach to decision making as opposed to the one size fits all method.

Statements 6 to 8 highlight that variant histology is a rare but worrisome pathological finding and should be confirmed by an expert genitourinary pathologist. In addition, due to the limited data demonstrating a high rate of up staging, these variant histologies should be managed aggressively with repeat resection in the cases for which bladder sparing is being considered, or preferably, with radical cystectomy.

Statements 9 to 11 address the issue of urinary biomarkers and their use in diagnosis and surveillance. While some urinary biomarkers may have improved sensitivity and specificity compared to cytology, none of the available evidence supports their use in replacing cystoscopic surveillance. Furthermore, specifically for low risk patients, urinary biomarkers should not be used during routine surveillance. However, urinary biomarkers may help in cases of equivocal cytology or assessing response to intravesical BCG.

Statements 12 to 14 discuss repeat resection, and advocate its use in patients with incomplete resection, high risk, high grade Ta disease and T1 disease.

Statements 15 to 21 provide an overview of intravesical therapy. Key elements include the use of single agent intravesical chemotherapy within 24 hours for patients with low or intermediate risk disease, without perforation or extensive resection, 6-week induction intravesical therapy (chemotherapy or immunotherapy) for intermediate risk and 6-week induction BCG for high risk disease (CIS, HG T1, high risk Ta).

It was emphasized that maintenance therapy may be offered for up to 1 year in intermediate risk patients who respond to BCG and should be administered for up to 3 years in high risk patients based on the results of EORTC 30962.⁶

Statements 22 to 26 address BCG relapse and salvage regimens. Patients with persistent or recurrent disease, or positive cytology after intravesical therapy, should undergo workup including upper tract evaluation and prostatic urethral biopsy to identify occult sites of disease. A second course of BCG can be offered to patients with persistent or recurrent CIS or Ta disease after induction BCG and, this second course may be 3 or 6 weeks in duration.

However, patients with HG T1 disease who do not respond to induction BCG should be offered radical cystectomy due to worse prognosis and increased risk of death from disease in...
Difficult Cases in High Risk Bladder Cancer: An Evidence-Based Approach

Michael S. Cookson, MD, MMHC, FACS, Course Director; Jeffery M. Holzbeierlein, MD and Hristos Z. Kaimakliotis, MD, Faculty

The treatment of patients with bladder cancer is a significant proportion of many urologists’ busy clinical and surgical practice. In fact, it has been estimated that bladder cancer is the second most prevalent urological cancer and the most expensive cancer to treat.1, 2 We are at a crossroads in health care delivery, and we are being asked to deliver value based care at a time when there is increasing scrutiny of the cost of care delivered. We have an increased appreciation of evidence-based medicine with the acknowledgement of improved outcomes when these clinical principles are applied to patient care. The AUA guidelines for nonmuscle invasive bladder cancer (NMIBC) were recently released.3 Thus, conditions are optimal for an instructional course designed to inform clinicians of the latest in evidence-based recommendations for the treatment of men and women with urothelial carcinoma of the bladder.

The format of this AUA2017 course involves clinical cases selected from our practice, with salient features and management issues highlighted. Expert faculty are asked to review the pertinent evidence-based literature and comment on management without knowing the ultimate outcome. The actual management of the case and outcome are then revealed, and a discussion of how the management may or may not have adhered to best practices follows. This often includes clinical pathways and guidelines in a practical and clinically relevant presentation format. The course is also available as an interactive audience response system to query the audience on their understanding of the evidence.

The first case involved a patient with high grade (HG) clinical stage Ta and CIS NMIBC. We reviewed the natural history of high grade disease, risk stratification based on the European Association of Urology risk calculation and the AUA NMIBC guidelines, the role of enhanced cystoscopy (narrow band imaging and Cysview®), and the use of maintenance bacillus Calmette-Guérin (BCG) in these cases.3-7 Areas of emphasis included the identification of high risk disease and the treatment implications.5 The potential role of maintenance BCG as demonstrated in the SWOG study were also reviewed.6 The benefits of enhanced cystoscopy were highlighted, particularly in terms of fluorescent cystoscopy, with improved cancer detection and improved recurrence-free survival.7 Finally, the incorporation of these concepts as they pertain to the AUA guidelines was emphasized.

The second case was an elderly patient with BCG unresponsive NMIBC. Points of emphasis included reviewing the definition of BCG unresponsive bladder cancer, and available treatment options including intravesical chemo-
therapy and salvage regimens. The role of radical cystectomy for patients who are fit and willing as well as outcomes of cystectomy were discussed. As this case included a patient who was elderly, the selective use of radical surgery, assessment of frailty, and its potential morbidity and impact on cancer control were reviewed.

The third case involved a patient with a micropapillary stage T1 tumor, which represents a particularly challenging subset. This allowed for a review of variant histology in general and triggers for pathology review. Also covered were the AUA guideline recommendations for repeat resection in T1 tumors, variant histology and HG lesions. Controversy surrounding the optimal management of micropapillary variant tumors was reviewed. Finally, response to intravesical therapy and the role and outcomes of radical cystectomy were thoroughly covered.

The next case was that of a patient with clinical T2-3NxM0 invasive bladder cancer. The goals for this case were to review optimal management, including the options of bladder preservation, radical cystectomy and neoadjuvant/adjuvant cisplatin based chemotherapy. In this scenario, despite neoadjuvant chemotherapy (NAC), the patient was ultimately found to harbor positive lymph nodes on final pathology after cystectomy. The outcomes of node positive cases after NAC platinum based therapy were discussed and salvage chemotherapy regimens were reviewed. This also extended to a robust discussion of some of the exciting results that have been reported with newer agents, including immunotherapy and checkpoint inhibitors (PD-1, PD-L1) in metastatic bladder cancer.

The fifth case involved a patient with invasive bladder cancer treated with radical cystectomy. The discussion revolved around an open vs robotic surgical approach. The enhanced recovery after surgery pathways with contemporary modifications for cystectomy were reviewed, including protein loading, avoidance of a mechanical bowel preparation, use of alvimopan and fluid restriction. This included a review of the morbidity of cystectomy, with 90-day perioperative complications. Also reviewed were available data on outcomes in terms of length of stay (LOS), complications, readmissions, oncology outcomes (margin status, recurrence data) and cost.

The last case was that of a patient in whom a HG upper tract tumor develops on surveillance for NMIBC, so the points covered included the management of HG urothelial cell carcinoma of the upper tract. The role of endoscopic and surgical management of the primary tumor were also discussed, as well as the potential role of cisplatin based chemotherapy before nephroureterectomy. The implications for possible chronic kidney disease following surgery were also addressed, given the high degree of baseline and postoperative chronic kidney disease in this patient population.

The management of NMIBC remains challenging. An increasing awareness of management based on risk stratification has been acknowledged. Not only does proper risk assessment aid patients in understanding their individual risk of recurrence and progression, but it helps guide clinicians in overall optimal management. There have been many new tools to aid in the treatment of these patients, including better urinary markers and enhanced imaging to improve detection. Not only can these urinary biomarkers assist in detection during surveillance, but we are now finding ways to use them to predict response to intravesical therapy such as BCG. The use of maintenance BCG in intermediate and high risk patients, coupled with better identification of those patients who are unresponsive to intravesical therapy, allow for the opportunity to implement salvage treatments and cystectomy earlier than traditionally possible. These issues and many more were illustrated while covering these clinical scenarios, keeping evidence-based principles in mind.

Invasive bladder cancer remains a potentially lethal disease. Optimal management is predicated on early identification, accurate staging and surgical extirpation often combined with platinum based chemotherapy. Advances in management in the perioperative period have resulted in a reduction in morbidity and LOS. Increasingly, the use of minimally invasive surgical techniques has been applied with a predictable reduction in pain, blood loss and LOS. Long-term oncologic efficacy comparing laparoscopic and robotic techniques is awaiting analysis of the results of ongoing studies.

The awareness among urological surgeons of the added value of neoadjuvant and adjuvant chemotherapy has been realized, and yet we are still limited by the efficacy of the therapy in this often chemoresistant disease state. The development of new and effective immune based therapy as front line therapy in some, for those ineligible or who have progression after cisplatin, have given new hope for patients with disease that has progressed beyond the limits of surgical cure. We are on the cusp of validation of biomarkers linked to pathology that will aid in guiding therapy by predicting the response to systemic therapy. Our course covered these and many other topics related to the comprehensive management of bladder cancer.

AUA/ASCO/ASTRO/SUO Guidelines 2017: Muscle Invasive Bladder Cancer

Jeffrey Holzbeierlein, MD, Course Director; Jonathan Rosenberg, MD and Jeff Michalski, MD, MBA, FACC, FASTRO, Faculty

Bladder cancer represents the fourth most common cancer in men and sixth most common in women. Approximately 77,000 new cases of bladder cancer were detected in 2016 with around 16,000 deaths.1 Of those presenting with newly diagnosed bladder cancer 25% have muscle invasive disease that is almost invariably fatal if left untreated.2,3

Unfortunately, the overall prognosis of patients with muscle invasive bladder cancer (MIBC) has not changed in the last 30 years. For patients undergoing cystectomy, survival rates are based on stage, with 20% to 30% recurrence rates for pathological stage pT2, 40% for pT3, greater than 50% for pT4 and approximately 70% for node positive disease.4,5 Most recurrences are within the first 2 years after cystectomy, and at this time most patients with recurrence after cystectomy are not cured with current systemic therapies.6

Other therapies for the treatment of MIBC include chemotherapy and radiation (XRT). Although there is 1 randomized controlled trial comparing trimodal therapy (transurethral resection [TUR] + chemotherapy + XRT) to cystectomy, the overall level of evidence comparing different treatments is poor. Thus, the panel for the AUA guidelines for MIBC included representatives from the AUA, ASCO (American Society of Clinical Oncology), ASTRO (American Society for Radiation Oncology) and SUO (Society of Urologic Oncology) as well as a patient advocate to consider the available evidence and make recommendations regarding the evaluation and management of nonmetastatic MIBC.

At the 2017 AUA annual meeting this course was held to present the first guidelines addressing muscle invasive bladder cancer. This session was moderated by the guidelines’ Vice Chair, Dr. Jeff Holzbeierlein, and included panelists Dr. Jeff Michalski from ASTRO and Dr. Jonathan Rosenberg from ASCO, both of whom served on the guidelines panel. A brief overview of the MIBC guidelines was also presented at the plenary session. This course involved a more in-depth discussion of the newly developed guidelines and specifically addressed the multidisciplinary development of the guidelines. In addition, participants were encouraged to ask questions regarding specific guideline recommendations.

Attendees of the MIBC course had the opportunity to see how the panel developed the MIBC guidelines, including a review of the strengths of evidence, how recommendations are made and the process for developing a guideline. The definitions of Expert Opinion and Clinical Principle were reviewed in order to clarify the strength of many of the recommendations in the guideline.

Initial Management and Staging

In terms of the actual guidelines statements, the panel began by reviewing the initial evaluation and counseling of the patients with muscle invasive bladder cancer. This included reviewing the decision making for the staging evaluation, as well as addressing specific patient concerns regarding treatment and the need for a multidisciplinary approach. The panel recommended chest imaging with a chest x-ray or computerized tomography (if the patient is a smoker), cross-sectional imaging of the abdomen and pelvis, and laboratory assessment. Questions from attendees regarding the use of positron emission tomography were addressed by the panel, who did not believe the evidence currently supported its routine use. The panel emphasized the importance of discussing the various impacts on quality of life of the treatments for bladder cancer.

Neoadjuvant Chemotherapy

Dr. Rosenberg then reviewed the guideline recommendations for neoadjuvant chemotherapy including the data that support its use, predominantly 2 large randomized trials.7,8 In addition, Dr. Rosenberg discussed contraindications...
to neoadjuvant chemotherapy as well as optimal regimens for neoadjuvant chemotherapy. Specifically he addressed the recommendation against the use of carboplatin chemotherapy in the neoadjuvant setting.

**Cystectomy**

The role of radical cystectomy in the management of MIBC was covered next, including the role of lymphadenectomy, the options as well as contra-indications to certain urinary diversions and the perioperative management of cystectomy cases. Based on currently available data, the panel recommended performing standard lymphadenectomy with the goal of removing at least 10 to 12 lymph nodes, as this is a surrogate for the completeness of the dissection. In determining eligibility for orthotopic urinary diversion, the panel recommended analysis of a frozen section of the urethra at the time of cystectomy. The panel also emphasized the need for improved perioperative management during cystectomy, including the use of pharmacological thromboprophylaxis and alvimopan, a mu-opioid receptor antagonist.

**Multidisciplinary Management**

Unique to this guideline and its presentation was the multidisciplinary representation from the AUA/SUO, ASTRO and ASCO. As part of the guidelines and the course, Drs. Michalski and Rosenberg presented the guideline panel recommendations regarding bladder preservation strategies, which included recommendations for patient selection for bladder preservation, a discussion of the various strategies and the followup of patients who undergo bladder preservation treatment for MIBC. Dr. Michalski further covered other recommendations on the use of radiotherapy while Dr. Rosenberg discussed the appropriate types of chemotherapy in bladder preserving strategies.

The data supporting the use of bladder preserving techniques were reviewed as part of this session as well. Specifically, the panel recommended trimodal therapy consisting of complete TUR, chemotherapy using either 5-fluorouracil and mitomycin or cisplatin, and concurrent radiotherapy as the optimal bladder preservation strategy. Dr. Michalski emphasized that the use of radiotherapy as a sole modality was not recommended for the management of MIBC but rather should be reserved for palliation. Recommendations for surveillance after bladder preservation include frequent cystoscopy and periodic cross-sectional imaging.

**Survivorship**

The panel briefly touched on the survivorship recommendations, under the direction of Diane Quale, the patient advocate on the panel. These recommendations include discussing quality of life issues with the patient and addressing healthy lifestyles, including smoking cessation and healthy eating and exercise. In addition, consultation with an enterostomal therapist when available was considered a critical component of the patient recovery.

**Future Directions**

Finally, the panel discussed some of the recommendations regarding variant histologies and future directions in the evaluation and management of MIBC. The panel recognizes that treatment options regarding variant histology are currently evolving, and that at this time the optimal management for most variant histologies remains unknown.

In addition, current trials such as the COXEN (co-expression extrapolation) trial will seek to identify optimal candidates for neoadjuvant chemotherapy and identify biomarkers for chemosensitivity, and these data are likely to change the guideline recommendations in the future.

The session concluded with a review of the MIBC treatment algorithm. Attendees had the opportunity to ask the panel members specific questions about the guidelines, including clarification of the specific recommendations as well as questions regarding the evidence used to create the guidelines. In addition, participation from radiation oncology, medical oncology, and urologic oncology provided insight into the panel’s thought processes, especially given the large number of Expert Opinions in the document.

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Management of Nonmuscle Invasive Bladder Cancer: Practical Solutions for Common Problems

Cheryl T. Lee, MD, Course Director; Ashish M. Kamat, MD, MBBS, FACS, J. Alfred Witjes, MD and Kamal S. Pohar, MD, Faculty

For more than a decade this course has provided a framework to manage common clinical predicaments in patients with nonmuscle invasive bladder cancer (NMIBC). With the backdrop of practice guidelines from the AUA and the EAU (European Association of Urology), the course faculty have provided practical solutions that clinicians can integrate into the office setting. Emphasis has been placed on evidence-based treatment of NMIBC, whenever possible, while offering insight into areas of practice that lack clear consensus or supportive evidence. This past year, using a format based on didactics, board preparation and discussion of real clinical cases, the course focused on a review of the 2016 AUA guidelines for NMIBC, risk based selection of intravesical therapy, toxicity management of these treatments and considerations necessary to use cystectomy.

AUA Guidelines: Diagnosis of Nonmuscle Invasive Bladder Cancer

The AUA guidelines for NMIBC have recently been updated and reflect several points that all urologists treating bladder cancer will want to know. An important emphasis of the guidelines is the risk stratification of patients (see Appendix). This schema provides a clear path for risk based diagnostic, treatment and surveillance recommendations, which begins with a comprehensive transurethral resection using key elements to optimize tumor staging, including visualization of detrusor muscle in the resection base and, whenever possible, the performance of a visually complete resection. Improved tumor detection and recurrence-free survival have been demonstrated with the use of enhanced cystoscopic techniques such as blue light cystoscopy. The use of photodynamic diagnosis not only increases the detection of Ta tumors by 16%, but also increases the detection of high risk T1 tumors and carcinoma in situ (CIS) up to 13% and 46%, respectively. The use of urinary markers is also reviewed in the guidelines. Clinicians should not use urinary biomarkers in place of cystoscopic evaluation. In addition, although the surveillance of intermediate and high risk patients should include urinary markers, the patient with low risk bladder cancer does not require routine use of a urinary biomarker or cytology during surveillance. But certainly markers can and should be used to assess response to therapy. Biomarkers may also be used to assess response to intravesical bacillus Calmette-Guérin (BCG) (UroVysion® fluorescence in situ hybridization [FISH]) and to adjudicate equivocal cytology (UroVysion FISH and ImmunoCyt™).

Re-staging transurethral resection of bladder tumor (TURBT) is also a focus of the 2016 guidelines as a method to enhance staging. Re-staging TURBT should be considered 1) whenever pursuing bladder preservation in a patient with variant histology; 2) for incomplete resection; 3) for high risk, high grade (HG) Ta (particularly high volume disease) and 4) in the setting of T1 disease, as re-staging practices can achieve diagnostic, prognostic and therapeutic benefit.

Choosing the Best Intravesical Agent: A Consideration of Risk Stratification

Understanding risk groups (and the related risks of recurrence and progression) is the basis of treating patients with NMIBC. These risk groups are comparable in the AUA and EAU guidelines. Low risk patients are those with small solitary low grade Ta lesions, high risk patients are more or less those with high grade or T1 lesions or CIS, and intermediate risk patients are in-between, such as those with recurrent multiple Ta lesions. Both the intermediate and high risk groups can be further subdivided with additional factors to tailor treatment. Finally, the worst high risk category refers to patients with BCG unresponsive disease, variant histology or prostatic urethra involvement.

In consideration of the risks associated with each category, there is suggested therapeutic advice across the risk strata. The guideline recommendation is for immediate post-TURBT instillation of chemotherapy in the low risk group, although we have to realize this strategy is not always done nor always possible. In the intermediate risk group a course of chemotherapy or BCG is recommended, with a maintenance schedule if no recurrence or major side effects. In the high risk group the clear suggestion is a 1 to 3-year maintenance BCG schedule.

Unfortunately, BCG response cannot be predicted, which is particularly problematic in times of BCG shortage. Treatment strategies in the context of BCG shortage include the use of chemotherapy in intermediate risk patients, and/or a reduction of the dose, number of instillations or the treatment schedule in high risk patients. In the highest risk category cystectomy should be considered. For patients unfit or unwilling to undergo cystectomy, alternatives include intravesical gemcitabine, BCG combined with interferon or radio frequency induced intravesical chemohyperthermia. However, experience is limited and efficacy still insufficiently proven. In all, the treatment of patients with NMIBC is well-defined within the available guidelines, but not always feasible in clinical practice, so it is good to be aware of viable alternatives.
BCG infection, which may require antituberculin therapy, oral steroids and/or consultation with Infectious Disease.

**When Should We Move to Cystectomy in Patients with NMIBC?**

In a patient with NMIBC we should move to radical cystectomy when bladder preservation results in a real loss of an opportunity to cure the patient. As recommended by various guidelines (AUA, EAU, International Bladder Cancer Group and International Consultation on Urological Diseases), patients with NMIBC should be stratified by risk of recurrence and progression into subgroups of low, intermediate and high. The high risk group must always be aware that radical cystectomy is an option, even at presentation. A subgroup of patients at highest risk has been recognized by the EAU guidelines in which radical cystectomy should not only be discussed but offered as an upfront choice. This includes patients with high grade/G3 (HG) T1 disease with concurrent bladder CIS; multiple, large and/or recurrent HG T1 disease; HG T1 disease with CIS in the prostatic urethra or with micropapillary variant of urothelial carcinoma.\(^6\) In addition, patients with “deep” T1 (ie T1b/c) and those with lymphovascular invasion (LVI) on transurethral resection (TUR) specimen should be considered for early cystectomy because they are at very high risk for progression.

HG T1 bladder cancer remains an area that is misunderstood by many physicians. It is important to recognize that T1 tumors are, by definition, invasive (into lamina propria). There is a significant risk of under staging (which is why re-staging TURBT is recommended by the guidelines) and of metastatic disease even without progression to T2. Thus, any patient with HG T1 tumor (especially those with the previously mentioned features) should be considered at high risk for progression despite prior treatment with BCG.\(^6\) Nonetheless, with optimal techniques (enhanced cystoscopy, repeat TUR, vigilant surveillance) many patients will achieve disease-free status in the bladder with intravesical therapy. However, the prostate (prostatic urethra and the ducts and acini) remains a sanctuary site where NMIBC can hide and must be evaluated carefully in any high risk patient, especially those who have recurrent disease. In patients who have invasion of the stroma, radical cystectomy alone is not enough. These patients should be considered for neoadjuvant chemotherapy since their risk of micrometastatic disease is significant.

The need for cystectomy must also be considered in the context of high grade recurrent disease despite adequate BCG. Patients who are BCG unresponsive have 1) persistent HG disease at 6 months despite adequate BCG treatment, 2) stage/grade progression at 3 months after induction BCG or 3) recurrence of HG disease within 6 months of last exposure to BCG (eg those on maintenance therapy). These individuals should be counseled that radical cystectomy remains the only treatment option with a well documented cure rate in this setting. This area remains one of intense research and drug development but no therapy has been shown to have consistent and durable long-term efficacy.
### Appendix. AUA Risk Stratification for Nonmuscle Invasive Bladder Cancer

<table>
<thead>
<tr>
<th>Risk Status</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low grade solitary Ta (≤ 3cm)</td>
<td>Low grade solitary Ta (&gt;3cm)</td>
<td>High grade Ta (&gt;3cm)</td>
<td></td>
</tr>
<tr>
<td>Papillary urothelial neoplasm of low malignant potential</td>
<td>Low grade Ta (multifocal)</td>
<td>High grade Ta (multifocal)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low grade Ta, recurrence within 1 year</td>
<td>High grade Ta, any recurrence</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High grade Ta (≤ 3cm)</td>
<td>High grade T1</td>
<td></td>
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<tr>
<td></td>
<td>Low grade T1</td>
<td>Any CIS</td>
<td></td>
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<td></td>
<td></td>
<td>Any LVI</td>
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<tr>
<td></td>
<td></td>
<td>Any variant histology</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Any BCG failure in high grade cancer</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Any high grade prostatic urethral involvement</td>
<td></td>
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</tbody>
</table>

Adapted from Chang et al.\(^1\)

Next Frontier: Immunotherapy for Bladder Cancer

Peter C. Black, MD, FACS, FRSC

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Immunotherapy has taken the entire field of oncology by storm in the last 5 years but for once bladder cancer has not been left behind. After decades without significant advances in systemic therapy for bladder cancer, a number of novel agents that help reactivate the patient’s antitumor immune response are under clinical development. The headlines are being dominated by checkpoint inhibitors, especially in the form of monoclonal antibodies that target PD-1, PD-L1 or CTLA-4 in tumor and/or immune cells (see figure).

Any interaction between an immune cell and a tumor cell or antigen-presenting cell involves a fine-tuned interplay between stimulatory and inhibitory signals to regulate the subsequent immune response. Tumors are able to exploit this regulatory machinery to ensure immune evasion, but checkpoint inhibitors can, in turn, unleash an effective antitumor immune response with dramatic clinical benefit.

The first trials to investigate checkpoint inhibitors have been in patients with metastatic urothelial carcinoma that has progressed despite prior platinum based chemotherapy (see table). Atezolizumab and nivolumab have demonstrated efficacy as first line therapy in platinum ineligible patients with metastatic urothelial carcinoma. Trials to test the efficacy of checkpoint blockade in first line platinum eligible patients are ongoing, and the optimal sequencing of chemotherapy and immunotherapy will be addressed in the near future. We know from the phase III pembrolizumab trial that the adverse effects with chemotherapy are greater, but in principle we want our patients to be able to receive both lines of therapy.

Atezolizumab and nivolumab are now approved by the FDA (Food and Drug Administration) in this disease state based on large, single arm, phase II trials.1, 2

In a phase III trial pembrolizumab was demonstrated to be superior to second line chemotherapy with respect to overall survival and, therefore, will also likely be approved soon.3 Durvalumab and avelumab have shown equally promising results in early phase trials.4, 5 All of these agents induce an objective response rate of approximately 20% and these responses are often durable.

One of the greatest unmet needs in bladder cancer care is the lack of options for patients who are ineligible for platinum based chemotherapy. Although not yet approved for these patients, blockade in first line platinum eligible patients are ongoing, and the optimal sequencing of chemotherapy and immunotherapy will be addressed in the near future. We know from the phase III pembrolizumab trial that the adverse effects with chemotherapy are greater, but in principle we want our patients to be able to receive both lines of therapy.

Although the excitement around checkpoint blockade has been enormous, the sobering reality is that 80% of patients do not demonstrate an objective response to these agents. However, single agent PD-1, PD-L1 or CTLA-4 inhibition is only the tip of the iceberg. There is a dizzying array of potential combinations between checkpoint blockade and other conventional (eg chemotherapy or radiation therapy) or...
novel therapies, and there are many other novel drugs under development that target other checkpoint molecules.

One of the first large trials that will report on combination therapy recently completed accrual. It tested in the first line metastatic setting chemotherapy vs durvalumab vs the combination of durvalumab (PD-L1 inhibitor) and tremelimumab (CTLA-4 inhibitor). Any benefit of combination therapy will need to be balanced carefully with potential toxicity.

The other natural development occurring with checkpoint blockade is its migration into earlier disease states. Trials are under way to test these agents before and after radical cystectomy for muscle invasive bladder cancer.

Three of the agents are also being tested in patients with bacillus Calmette-Guérin (BCG) unresponsive nonmuscle invasive bladder cancer with the intent of avoiding cystectomy and preserving the bladder. Since BCG is itself an immunotherapy, these trials build on the hypothesis that the checkpoint regulated immune evasion contributes to treatment failure.

The excitement around immunotherapy for bladder cancer has been buoyed by the good safety profile of these agents. There is no question that immune regulated adverse events can occur and can be life threatening, so vigilance is required at all levels of care with patients on immunotherapy. Providers who are likely to have regular contact with these patients need to be familiar with some of these toxicities and their management.

As immunotherapy migrates into earlier disease states, extra precautions are necessary to ensure that the risk-benefit balance is maintained. Furthermore, it remains to be seen if any urologists will adopt regular administration of checkpoint inhibitors, which in their current forms are usually administered by intravenous infusion every 2 to 4 weeks. The primary barrier is not the infusion itself, as infusion related reactions are infrequent, but rather the management of subsequent immune related toxicities.

With only 20% of patients responding to PD-1 and PD-L1 blockade, biomarkers are required to predict which patients are likely to respond. Although multiple candidate markers exist for this purpose, none has proven clinically useful at this point.

Immunohistochemical (IHC) staining for PD-L1 in tumor cells and tumor infiltrating immune cells has received the most attention. Unfortunately each pharmaceutical company has its own companion IHC test with different antibodies, diverse staining methods and variable scoring systems. As a result, the clinical implications of PD-L1 staining remain unclear.

Efforts to harmonize PD-L1 staining are ongoing but in the meantime PD-L1 staining is not considered adequate to guide patient selection. Other promising biomarkers include RNA signatures (eg molecular subtypes of bladder cancer) and DNA mutation rates.

In a short time immunotherapy has established itself as a key component of the treatment algorithm for patients with bladder cancer. This field will continue to evolve at a rapid pace and it will be important for urologists to keep abreast of these developments.

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See you in San Francisco!