HHS Public Access

Author manuscript

JAMA Oncol. Author manuscript; available in PMC 2021 June 18.

Published in final edited form as:

JAMA Oncol. 2019 December 01; 5(12): 1790–1798. doi:10.1001/jamaoncol.2019.4114.

Eligibility and Radiologic Assessment in Adjuvant Clinical Trials in Bladder Cancer

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Author Contributions: Drs Apolo and Agrawal had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Obtained funding: Apolo.

Administrative, technical, or material support: Apolo, Kim, Inman, Steinberg, Bagheri, Krishnasamy, Bangs, Liu, Cross, Pazdur, Blumenthal, Agrawal.

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Abstract

OBJECTIVE—To harmonize eligibility criteria and radiographic disease assessments in clinical trials of adjuvant therapy for muscle-invasive bladder cancer (MIBC).

METHODS—National experts in bladder cancer clinical trial research, including medical and urologic oncologists, radiologists, biostatisticians, and patient advocates, convened at a public workshop on November 28, 2017, to discuss eligibility, radiographic entry criteria, and assessment of disease recurrence in adjuvant clinical trials in patients with MIBC.

RESULTS—The key workshop conclusions for adjuvant MIBC clinical trials included the following points: (1) patients with urothelial carcinoma with divergent histologic differentiation should be allowed to enroll; (2) neoadjuvant chemotherapy is defined as at least 3 cycles of neoadjuvant cisplatin-based combination chemotherapy; (3) patients with muscle-invasive, upper-tract urothelial carcinoma should be included in adjuvant trials of MIBC; (4) patients with severe renal insufficiency can enroll into trials using agents that are not renally excreted; (5) patients with microscopic surgical margins can be included; (6) patients should undergo a standard bilateral lymph node dissection prior to enrollment; (7) computed tomographic (CT) imaging should be performed within 4 weeks prior to enrollment. For patients with renal insufficiency who cannot undergo CT imaging with contrast, noncontrast chest CT and magnetic resonance imaging of the abdomen and pelvis with gadolinium should be done; (8) biopsy of indeterminate lesions to evaluate for malignant disease should be done when feasible; (9) a uniform approach to evaluate indeterminate radiographic lesions when biopsy is not feasible should be included in any trial design; (10) a uniform approach to determining the date of recurrence is important in interpreting adjuvant trial results; and (11) new high-grade, upper-tract primary tumors and new MIBC tumors should be considered recurrence events.

CONCLUSIONS AND RELEVANCE—A uniform approach to eligibility criteria, definitions of no evidence of disease, and definitions of disease recurrence may lead to more consistent interpretations of adjuvant trial results in MIBC.

As adjuvant therapies continue to be explored in urothelial carcinoma (UC), patient populations enrolled may be heterogeneous owing to variability in eligibility criteria and subpopulations enrolled. The eligibility criteria used for trials of novel agents are often the same as those used for prior adjuvant chemotherapy trials, but these criteria may be unnecessarily prohibitive when applied to trials using newer agents, such as checkpoint inhibitors. Other areas of potential heterogeneity include the radiographic definitions used to enroll and assess patients during trials, methods to define the date of recurrence, and management of patients diagnosed with non–muscle-invasive disease in the remaining urothelial tract during adjuvant treatment. Having a uniform approach to these issues across trials will allow for more consistent interpretation of adjuvant trial results.

Initiative

The US Food and Drug Administration and the National Cancer Institute, with support from the Society of Urologic Oncology, convened a public workshop on November 28, 2017, at the National Institutes of Health in Bethesda, Maryland, to discuss protocol criteria for adjuvant clinical trials of muscle-invasive bladder cancer (MIBC) and kidney cancer. This effort focused on 4 topics regarding MIBC adjuvant trials: (1) the role of patient and disease

characteristics, (2) defining radiographic eligibility, (3) defining disease recurrence, and (4) management of non–muscle-invasive bladder cancer (NMIBC). Multiple virtual meetings were used to outline these topics, and major issues were discussed further at the workshop with input from investigators, patient advocates, biostatisticians, industry representatives, regulators, and the public. This report summarizes discussions from the workshop and associated meetings. The kidney cancer component of the workshop addresses many of these same issues and contains complementary material (S.A., unpublished information, September 2019). The key workshop discussion points are summarized in Table 1.[1] Some recommendations in Table 1 are not included in the text.

Patients and Disease Characteristics

Histologic Subtypes

Histologic variants are seen in 10% to 25% of bladder cancers.[2] Many definitions for variant histologic bladder cancer exist, but the simplest is anything other than pure urothelial carcinoma (UC). Histologic classifications are based on morphologic features shown on routine hematoxylin-eosin sections. Emerging genomic data will potentially help to better characterize these tumors and classify them into distinct subtypes.[3,4]

Some variants behave similarly to conventional UC; others, however, are more aggressive. Determining if variants have differing responses to therapy compared with conventional UC has been challenging, which has led to general exclusion of variant histologic characteristics in adjuvant trials. Patients with predominant (≥50%) UCs who have a component of variant histologic characteristics should be included in adjuvant trials (Table 1). To account for variations in response, trials could perform subset analyses if sufficient numbers of patients are enrolled. However, patients with pure non-UC histologic characteristics, especially mixed neuroendocrine/small cell tumors, if included, should be analyzed separately. The outcomes and correlative studies from adjuvant trials that include patients with variant and pure non-UC histologic characteristics will be critical to advancing therapies for these rare bladder tumors.

Prior Neoadjuvant Therapy

Despite level 1 evidence supporting the use of neoadjuvant cisplatin-based chemotherapy in MIBC, the optimal regimen and number of cycles have not been defined, and there is limited information regarding how many cycles of neoadjuvant cisplatin-based chemotherapy are optimal. A comparative study that included 212 patients from 28 centers reported that a median of 3 cycles of neoadjuvant chemotherapy with gemcitabine and cisplatin vs combined methotrexate, vinblastine, doxorubicin, and cisplatin achieved similar and promising pathologic complete response rates.[5] Based on this information, if neoadjuvant chemotherapy is given, a minimum of 3 cycles of neoadjuvant cisplatin-based chemotherapy, with a cisplatin dose of at least 70 mg/m^2/cycle, should be given (Table 1). This criterion is reasonable for eligibility in clinical trials exploring novel adjuvant therapies in patients with MIBC with a substantial tumor burden (pT2+ and/or pN+) after neoadjuvant treatment. There are insufficient data to determine what constitutes adequate total doses of chemotherapy. To our knowledge, there is no evidence to support a survival benefit with

non–cisplatin-based neoadjuvant chemotherapy. Thus, patients who have received non–cisplatin-based or less than 3 cycles of cisplatin-based neoadjuvant treatment should be managed and stratified as if they had not received neoadjuvant chemotherapy, and their eligibility should be based on postcystectomy pathologic stage (Table 1).

Muscle-Invasive, Upper-Tract UC

Adjuvant trials on MIBC have generally excluded patients with muscle-invasive upper-tract UC. Patients with muscle-invasive upper-tract UC should be included in adjuvant trials for MIBC because they too can potentially benefit from these therapies and important information can be gathered from clinical trials on their outcomes (Table 1). If possible, patients with upper-tract vs lower-tract UC should be stratified in randomized trials to account for potential differences in outcomes. To our knowledge, there is no evidence that systemic adjuvant therapy in non–muscle-invasive upper-tract tumors improves outcome.

Surgical Considerations for Eligibility

Positive Surgical Margins

Positive surgical margins in bladder cancer are associated with development of metastatic disease, and the lowest rates of overall and disease-free survival.[6,7] Patients with microscopic (R1) margins should be included in MIBC adjuvant trials because excluding these patients would disallow those at the greatest risk of recurrence to potentially benefit from adjuvant therapy and including them will serve to collect information on this subset of patients (Table 1). There may be a benefit to stratifying these patients, given a potentially worse outcome. However, it is not clear if patients with grossly positive (R2) soft-tissue margins should be included in an adjuvant setting (Table 1).

Pelvic Lymph Node Dissection

Pelvic lymph node dissection is crucial for accurate staging. Retrospective data suggest a possible therapeutic benefit depending on the extent of lymph node dissection.[8,9] A randomized clinical trial[10] and a National Cancer Institute cooperative group trial (SWOG-S1011; NCT01224665) were designed to determine the therapeutic role of extended vs standard pelvic lymph node dissection in MIBC. A German trial that randomized 401 patients (203 limited and 198 extended) to lymph node dissection found no difference in 5-year, recurrence-free survival (59% vs 65%, $P = .36$) at a median follow-up of 43 months.[10] The 5-year overall survival rate was 49.7% in the limited group compared with 58.9% in the extended group ($P = .12$). The ongoing National Cancer Institute cooperative group trial may help to clarify the benefit of extended lymph node dissection. Standard pelvic lymph node dissection, including bilateral external and internal iliac and obturator lymph nodes, will identify patients who have lymph node metastasis but may underestimate the extent of lymph node involvement.[11,12] Given the unknown therapeutic value of extended over standard lymph node dissection at this time, patients should have, at minimum, a bilateral standard pelvic lymph node dissection for eligibility in adjuvant trials (Table 1). Other surgical considerations, including lymph node counts and density, may also be considered as stratification variables to be used in clinical trials.

Timing and Duration of Adjuvant Therapy

Few data exist regarding the ideal time to initiate adjuvant therapy. A study evaluated postoperative complications after radical cystectomy and their association with the timing and ability to receive adjuvant chemotherapy. Of 1142 patients who underwent radical cystectomy, 30% had Clavien-Dindo grade 2 to 5 complications 6 to 12 weeks after surgery, leading to the conclusion that these patients would not have been eligible for adjuvant chemotherapy.[13] This finding suggests that, after radical cystectomy, initiation of adjuvant therapy may be delayed 3 months or longer for some patients, given the high complication rate associated with the procedure.[13] One to 4 months post radical cystectomy is a reasonable time for enrollment in an adjuvant trial (Table 1).

Radiologic Considerations

Imaging in adjuvant trials poses inherent challenges, as there is substantial variation in radiologic interpretation of recurrent and metastatic cancer, and there are no standardized radiographic criteria for identifying site-specific recurrences. In addition, imaging commonly demonstrates equivocal findings, including the development of a secondary cancer, and biopsy is not always feasible (biopsy considerations are presented in the Box[14–18]). Cultivating uniformity in these elements will help to optimize the scaling of data in multi-institutional clinical trials.

Radiologic Practices

Computed tomographic imaging of the chest, abdomen, and pelvis with intravenous contrast should be performed within 4 weeks prior to trial enrollment. Computed tomography is considered the imaging modality of choice during the entirety of the trial so long as it is feasible (Table 1), thereby designating other imaging modalities, such as magnetic resonance imaging (MRI) or positron emission tomography as auxiliary or problem-solving imaging tools. The preference for CT imaging is because of its availability, ability to standardize imaging acquisition technique, and ability to adequately visualize the most common manifestations of recurrent and metastatic UC.[19–21] Computed tomographic imaging thereby offers many advantages in broad implementation, and, while meta-analyses have shown that MRI and positron emission tomography may offer superior specificity or negative predictive value, the differences are not substantial when directly compared with CT imaging.[22] For patients with renal insufficiency who cannot undergo CT imaging with contrast, noncontrast chest CT imaging and MRI of the abdomen and pelvis with gadolinium should be done.

Trials should adhere to imaging acquisition, display, and radiologic interpretation technique as advised by the Quantitative Imaging Biomarkers Alliance (Table 1).[1] Uniformity in imaging acquisition and display is essential for standardizing radiologic criteria that use size measurement as a metric, as studies have shown that differences in slice display not only affect the detection rate of lesions,[23] but can also lead to statistically significant differences in size measurement of lesions.[24]

Radiologic Evaluation of Clinical Trial Eligibility

There are currently no standardized criteria to adjudicate equivocal radiologic findings when evaluating patients for adjuvant trial eligibility. The workshop addressed this issue and included a review of available literature on tumor assessment imaging. Published imaging guidelines from the Quantitative Imaging Biomarkers Alliance,[1] in addition to principles outlined in Response Evaluation Criteria in Solid Tumors,[25] support the following general radiologic practices to aid in interpreting equivocal radiologic findings during initial evaluation:

1. When no prior imaging exists, the equivocal lesion should be assumed to be benign if it measures less than 1.0 cm (long axis for all non–lymph node lesions, short axis for lymph nodes). This 1.0-cm size threshold represents the general consensus in radiologic practice as to what size is deemed reasonably sensitive and specific to identify potential cancer,[19,26] as well as what size is required to reliably characterize a lesion on CT imaging.[1]
2. Lesions measuring 1.0 cm or more (long axis for all non–lymph node lesions, short axis for lymph nodes) should be regarded as suspicious for malignant disease. If no alternative clinical explanation beyond cancer exists, customized radiologic workup of the lesion or further initial evaluation after an appropriate amount of time—as outlined by radiologic guidelines regarding the resolution of indeterminate findings—is warranted prior to enrollment. Alternatively, biopsy may be warranted at the discretion of the investigator. Table 2 summarizes the approach to these findings.[27,28]

Radiologic Assessment of Disease Recurrence

Response Evaluation Criteria in Solid Tumors were developed to standardize the approach to disease assessments in patients with existing disease. However, there are no specific criteria for identifying new radiographic lesions,[25] and thus no standard approach currently exists to assess for recurrence in patients who are presumed to be free of disease in an adjuvant trial. This issue warrants review, as the application of varying response criteria may affect trial outcomes.[25,29]

Workshop discussion centered around developing a uniform approach to assess for recurrence on surveillance imaging to ensure accuracy and consistency in reporting outcomes when biopsy is not feasible. The result of this discussion was a proposed model designed with principles of the Response Evaluation Criteria in Solid Tumors[25] in mind and supported by technical standards as defined by the Quantitative Imaging Biomarkers Alliance.[1] Key points were (1) any new lesion 1.0 cm or larger that was absent on initial evaluation; (2) any preexisting lesion smaller than 1.0 cm demonstrating 50% or more growth on 2 consecutive radiologic examinations with 5 mm or more absolute increase or 1.0 cm or larger demonstrating 50% growth on a single examination; or (3) multifocal lesions measuring less than 1.0 cm that demonstrate geographic distribution or radiographic and/or metabolic features that are pathognomonic for metastatic disease can all be reasonably considered as unequivocal recurrence, assuming the complete exclusion of an alternative clinical explanation beyond cancer (Table 2).

Designating recurrence of small tumors (<1.0 cm) or a single lesion 1.0 cm or larger based on these criteria may be problematic, as this designation may lead to an overestimation of recurrence. However, these proposed size criteria represent a rate of growth that substantially outpaces the volumetric doubling rate of metabolically indolent processes, thereby achieving a level of specificity reasonable for a diagnosis of unequivocal recurrence in the absence of histologic confirmation. Protocols using different numeric thresholds may be reasonable but should be consistent so that there is accurate and uniform application of the trial criteria.

Defining Date of Recurrence

Various methods may be used to define the date of recurrence on an adjuvant trial. Backdating the recurrence date to the time a new lesion first appeared on imaging could potentially identify patients who are ineligible for a trial on a retrospective basis, as progression might be backdated to imaging findings that did not meet criteria for disease at baseline or the first appearance of a lesion may not be entirely clear. These issues introduce inconsistency into the date determination.

Assigning the date of recurrence as the time at which specific radiologic criteria are met avoids these issues, and applying criteria, such as those outlined in Table 2, to specific sites of recurrence is a more consistent method for determining the date of recurrence. However, this method lacks temporal accuracy with respect to the first instance of disease recurrence. There was no agreement at the workshop on which method should be used, but it was agreed that whichever method is used should be clearly stated in the protocol and followed to ensure consistent and accurate application of the trial criteria (Table 1).

Recurrence can also be dated to the time of a positive biopsy, if available, or at the time of investigator-assessed clinical progression. When a radiologic and histopathologic diagnosis date are both available, the date of radiologic diagnosis is preferred, because biopsies are typically prompted by preceding radiologic findings. Additional biopsy considerations are summarized in the Box.

Managing New Urothelial Tract Cancers

Patients on adjuvant MIBC trials are at risk not only for metastases, but also for recurrent or second primary tumors arising at new locations in the remaining urothelial tract. Diagnostic studies used to detect local urothelial cancer recurrence (Table 3)[30–41] should be considered and standardized during clinical trial design.

Do new UC primary cancers represent treatment failure? There are 2 opposing views on whether a urothelial second primary cancer in a patient undergoing treatment for MIBC represents treatment failure. The strict viewpoint defines any UC that occurs while a patient is undergoing systemic therapy as both a recurrence and a progression event, implying that the patient’s tumor has not responded to treatment and that treatment should stop. The benefit of this definition is that it applies equally to all UC locations and stages and is therefore simple to implement and interpret. That said, clinicians have observed complete and durable resolution of disease after systemic therapy for MIBC, only to witness recurrence of NMIBC tumors several years later that are successfully salvaged with

transurethral resection and intravesical therapy. The flexible viewpoint defines urothelial recurrence as a recurrence event, but only certain urothelial recurrences as progression events. Both of these views were addressed at the workshop, and discussion resulted in the following:

- There was agreement that all new, high-grade, upper-tract tumors and all new MIBC tumors should be considered progression events for the disease-free survival end point (Table 1).
- It is not evident if new primary tumors that are stage T1 or less should be defined as progression events for the disease-free survival end point. For example, many investigators believe that NMIBC (≤T1 stage) recurrence in a patient with MIBC is not a progression event, and the patient should be allowed to continue on trial after management of the tumor with transurethral resection with or without adjuvant intravesical therapy. There was no agreement on this issue, but it was agreed that management of these patients should be prospectively addressed and specified in protocols (Table 1).
- There was agreement that patients with a tumor recurrence in the remaining urothelium that is both low-grade and non–muscle-invasive can remain on trial provided the recurrence is manageable endoscopically (Table 1). However, if a low-grade NMIBC is too large or located in a difficult anatomic location and is consequently not amenable to endoscopic management, then the patient should be withdrawn from the trial. For intermediate- and high-risk NMIBC, the same considerations apply, with the additional consideration that patients receiving standard-of-care intravesical therapy be allowed to continue on trial. However, the appropriateness of continuing a systemic agent in conjunction with BCG or other intravesical therapy requires further discussion and evidence generation (Table 1).

Considerations for the Patient

There are many aspects of clinical trials and their conduct that are concerning to patients. The following points were agreed upon at the workshop:

- Patients with evidence of substantial disease burden and no alternative explanation for these lesions may reasonably be excluded from biopsy procedures that are intended to confirm recurrence to avoid unnecessary risk of an adverse event (Table 1).
- Seeking biopsies solely for the purposes of research should be carefully balanced with the best interests of the patient and should be clearly specified as supplemental to standard care during informed consent (Table 1).
- Patients often favor trial designs that eliminate the use of placebo, more heavily weight arms with an active agent, or allow crossover where justified by trial data (Table 1).

- There are cases in which patient and investigator unblinding are warranted after cessation of study treatment, such as when managing toxic effects or deciding on an appropriate next therapy (Table 1).

Planning for the Future

Implementing a uniform approach to eligibility criteria and definitions of residual and recurrent disease in adjuvant MIBC clinical trials may allow for less variability in trial conduct. Because data are currently lacking to support specific radiographic criteria, these definitions will require adjustment as more data become available, and the US Food and Drug Administration recommends continuing dialogue during trial design and development. However, a common approach and uniform application of trial criteria can still yield great benefit in conducting adjuvant trials. In considering the conduct of adjuvant MIBC trials, the scientific community must account for the rapidly changing landscape in bladder cancer and recognize the need for continued dialogue among various stakeholders.

Funding/Support:

This work was supported by the Intramural Research Program of the Center for Cancer Research, National Cancer Institute, National Institutes of Health and the Memorial Sloan Kettering Cancer Center P30 CA008748 grant.

Role of the Funder/Sponsor:

The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Conflict of Interest Disclosures:

Dr Milowsky reported receiving grants from Acerta Pharma, Astellas, Bristol-Myers Squibb, Incyte, Merck, Pfizer, Roche/Genentech, Seattle Genetics, Clovis Oncology Inc, Inovio Pharmaceuticals, AstraZeneca, and X4 Pharmaceuticals and personal fees from Rainier Therapeutics and Asieris during the conduct of the study. Dr Kamat reported receiving other support from FKD Industries; personal fees and other support from Merck, Bristol-Myers Squibb and Photocure; personal fees from Arquer, MDxHealth, Theralase, Medac, Asieris, Abbott Molecular, US Biotest, Ferring, Imagin, Eisai, BioClin Therapeutics, Cold Genesys, Roviant, and Sessen Bio; and grants from CEC Oncology outside the submitted work; in addition, Dr Kamat held a patent to CyPRIT (Cytokine Predictors of Response to Intravesical Therapy) jointly with The University of Texas MD Anderson Cancer Center and serves on the editorial boards of the European Urology Oncology *Journal of Urology* and *UroToday*, with annual honorariums. Dr Sweis reported receiving personal fees from Bristol-Myers Squibb, Exelixis, Mirati, AstraZeneca, Eisai, and Puma, as well as grants from EpiVax Oncology outside the submitted work. Dr Maher reported receiving personal fees from DataRevive outside the submitted work and now is employed by a regulatory consulting company, DataRevive. (This article was completed prior to assuming this position.) Dr Lerner reported receiving personal fees from Vaxiion, Anchiano Therapeutics, Incyte, Roche/Genentech, Ferring, Nucleix, Dava Oncology, MSD Korea, QED, and MiR Scientific outside the submitted work; grants and personal fees from UroGen; and grants from FKD, Endo, and Viventia outside the submitted work; in addition, Dr Lerner held a patent to TCGA classifier pending. Dr Bajorin reported receiving personal fees and other support from Bristol-Myers Squibb and Merck during the conduct of the study; as well as personal fees from Genentech, EMD Serono, Fidici Farmaceutici, AstraZeneca, Pfizer, Roche, and Eli Lilly outside the submitted work. Dr Rosenberg reported receiving personal fees and other support from Seattle Genetics, Astellas, Merck, Roche/Genentech, Bayer, AstraZeneca, Chugai, QED, and Bristol-Myers Squibb; personal fees from UpToDate, Eli Lilly, Inovio, Bioclin/Ranier, Adicet Bio, Sensei Biotherapeutics, Pharmacyclics, GSK, Janssen, and Western Oncolytics; as well as other support from Illumina outside the submitted work; in addition, Dr Rosenberg had a patent to predicting cisplatin sensitivity pending. No other disclosures were reported.

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Box.

Biopsy Considerations for Adjuvant Bladder Cancer Trials

- Biopsy remains the standard for determining recurrent cancer and provides concrete evidence for the end point of relapse-free survival.
- Trials should abide by national medical society practice guidelines that specifically address tissue biopsy. The Society of Interventional Radiology and the Cardiovascular and Interventional Radiological Society of Europe both provide guidelines for percutaneous needle biopsy.[14,15]
- If possible, discuss potential biopsies with at least 2 interventional radiologists in a multidisciplinary setting to increase the likelihood that each biopsy is held to uniform standards of risk threshold.[16]
- Because lymph nodes are the most common site of metastatic disease in urothelial carcinoma and are the most likely lesions to have equivocal features, procedural risk stratification based on node location is important to optimize tissue yield and minimize risk (low risk: superficial/subcutaneous sites; moderate risk: all intrathoracic and intraabdominal sites except renal; high risk: renal biopsy).[14,17]
- Percutaneous needle biopsy of retroperitoneal and pelvic lymphadenopathy has been shown to be safe and effective even with the use of adjunctive maneuvers for lymph node stations that are more challenging to biopsy.[18]

Table 1.

Summary of Workshop Discussion on the Conduct of Adjuvant Bladder Cancer Trials

Section	Workshop Discussion Points
Patient and Disease Characteristics	
Histologic subtypes	• Patients with predominant UC who have a component of variant histologic characteristics should be included in adjuvant trials. However, patients with pure, non-UC histologic characteristics, especiallymixed neuroendocrine/small cell tumors, if included, should be analyzed separately.
Prior neoadjuvant therapy	•At least 3 cycles of neoadjuvant cisplatin-based chemotherapy with a planned cisplatin dose of 70 mg/m^2/cycle is a reasonable eligibility criterion. • Patients who have received non-cisplatin-based or less than 3 cycles of cisplatin-based neoadjuvant treatment should be managed/stratified as having received no neoadjuvant chemotherapy, and their eligibilityshould be based on postcystectomystage.
Site of disease	• Patients with muscle-invasive upper-tract UC should be included in adjuvant trials.
Surgical considerations	•Patients with microscopic positive margins (R1) should be eligible, although statistical stratification may be considered. • It is not clear if gross positive margins (R2) should be included in studies. • Bilateral (standard) lymph node dissection is both favored and sufficient for accurate staging information.
Timing of adjuvant therapy	• Adjuvant therapy can be initiated as soon as the patient recovers from surgery, with a goalof 1to4 months postsurgery.
Duration ofadjuvanttherapy	• The length of checkpoint inhibitor therapy in adjuvant clinicaltrials of bladder cancer is not known owing to lack of data. Future trials could further examine duration of treatment.
Radiologic Considerations	
Radiologic imaging post-surgery	• Cross-sectional imaging of the chest, abdomen, and pelvis with IV contrast should be done within 4 wk prior to entering an adjuvant trial.
Principles of serial imaging	•Patients' prior imaging examinations should be archived and should include as many examinations as possible, including reports anda clinicalhistory documenting any prior acute and chronic diseases and prior surgeries and interventions. • CT imaging with contrast is the imaging modality of choice, when feasible. • Trials should aim to adhere to imaging acquisition, display, and radiologic interpretation technique as advised by the Quantitative Imaging BiomarkersAlliance.[1]
Defining radiographic eligibility for adjuvant bladder cancer trials and radiographic recurrence	•Biopsy should be done, when feasible, to determine if anymalignant disease is present. • Common thresholds to the radiologic assessment of patients for trial eligibilityand progression of disease should be implemented (Box).
Defining date of recurrence	• Backdating scans to when a new lesion was initiallynoted on imaging is considered as the most temporally accurate manner to assess the date of recurrence but introduces inconsistency. Using the date when prespecified size criteria are met (Box) is considered more consistent but lacks temporalaccuracy. Whichever method is used should be applied consistently and accurately throughout the trial.
Managing New Urothelial Cancers Within the Urothelial Tract	
Second primary cancers	•All new high-grade upper-tract primarytumors and all new muscle-invasive bladder cancer tumors are considered as events for the disease-free survival end point. • It is not clear whether new bladder second primary tumors that are ≤T1 category should be counted as an event for the disease-free survival end point. • Patients with tumors that are both low-grade and non-muscle-invasive could remain on trial if they can be managed endoscopically.
Urethralsecond primary tumors	• Patients with non-muscle invasive tumors manageable either endoscopically or with urethrectomy may remain on study. Patients with muscle-invasive recurrences should be removed from the trial and counted as disease recurrence.
Urine test utilization	• Trials should specify if urine tests should be used for post-operative surveillance and, if so, the specific test and testing interval required.
Augmented endoscopy	• Standard-of-care guidelines for endoscopic surveillance should be followed and defined at the start of the trial.

Section	Workshop Discussion Points
Random bladder biopsies	• Trials should specify whether random bladder biopsies should be obtained or not obtained to rule out occult carcinoma in situ. Further evidence is needed to inform whether this should be done for all patients with intact bladders.
Systemic agents and BCG vaccine	• Further evidence is needed to inform whether it would be appropriate to continue a systemic agent in conjunction with BCG or other intravesical therapy.
Considerations for the Patient	
Rare cancers	• There is concern about the consistency of histologic subtype classification/diagnosis and its potential effect on enrollment.
Biopsy	• Taking biopsies solely for the purposes of research should be carefully balanced with the best interests of the patient.
Placebo	• Trial designs that eliminate the use of placebo, more heavily weight the arm with an active agent, or allow crossover (where justified by trial data) are favored by patients.
Blinding	• Patients agree to blinding; however, they should be unblinded under certain circumstances.

Abbreviations: CT, computed tomographic; UC, urothelial carcinoma.

Table 2.

Radiologic Considerations for Evaluating Patient Eligibility During Initial Evaluation and Unequivocal Disease Recurrence During Adjuvant Trial Imaging Surveillance

Anatomic Location	Initial Evaluation: Findings Warranting Customized Radiologic Workup, Repeat Radiographic Evaluation, or Biopsy Prior to Enrollment	Adjuvant Trial Surveillance: Findings Qualifying as Unequivocal Disease Recurrence	Additional Workshop Discussion Points
Lung	Indeterminate pulmonary nodule ≥1.0 cm long axis	•New nodule ≥1.0 cm that was absent on initial evaluation • Preexisting nodule: • If <1.0 cm in previous examination, demonstrating >50% growth in long axis on 2 consecutive examinations with ≥5 mm absolute increase • If ≥1.0 cm in previous examination, demonstrating >50% growth in long axis on a single examination • Multifocalnodules measuring <1.0 cm that demonstrate geographic distribution or radiographic and/or metabolic features pathognomonic for metastatic disease	• Guidelines such as those published by the Fleischner Society[27] and the American College of Radiology Incidental Findings Committee[28] should be reviewed and may be helpful when evaluating indeterminate lesions on a retrospective basis on imaging performed prior to initial evaluation for trial, with the understanding that these guidelines were designed with the assumption that the patient has no underlying cancer.
Lymph nodes	Lymph node ≥1.0 cm short axis	•New lymph node ≥1.0 cm that was absent on initial evaluation • Preexisting lymph node: • If <1.0 cm in previous examination, demonstrating >50% growth in short axis on 2 consecutive examinations with ≥5 mm absolute increase • If ≥1.0 cm in previous examination, demonstrating >50% growth in short axis on a single examination	•Lymph nodes ≥1.0 cm but <1.5 cm in the short axis are suspicious; however, they can be difficult to interpret, and may not be convincing enough to call recurrence on imaging alone. • Nodes ≥1.5 cm in the short axis are considered highly suspicious for malignant disease involvement, especially when exhibiting growth on multiple scans.
Liver	Indeterminate lesion ≥1.0 cm long axis	•New lesion ≥1.0 cm that was absent on initial evaluation • Preexisting lesion: • If <1.0 cm in previous examination, demonstrating >50% growth in long axis on 2 consecutive examinations with ≥5 mm absolute increase • If ≥1.0 cm in previous examination, demonstrating >50% growth in long axis on a single examination • Multifocal lesions measuring <1.0 cm that demonstrate geographic distribution or radiographic and/or metabolic features pathognomonic for metastatic disease	• Any new enhancing lesions, even those <1.0 cm, are considered suspicious.
Other solid visceral organs (including spleen, pancreas, adrenal glands, and kidneys) and peritoneum, omentum, or mesentery	Indeterminate lesion ≥1.0 cm long axis	•New lesion ≥1.0 cm that was absent on initial evaluation • Preexisting lesion: • If <1.0 cm in previous examination, demonstrating >50% growth in long axis on 2 consecutive examinations with ≥5 mm absolute increase • If ≥1.0 cm on previous examination, demonstrating >50% growth in long axis on a single examination • Multifocal lesions measuring <1.0 cm that demonstrate geographic distribution or radiographic and/or metabolic features pathognomonic for metastatic disease	• Any new and/or enhancing mass in the abdominal cavity on CT imaging or MRI is considered suspicious, especiallywhen associated with lymphadenopathy.
Tumor resection bed	Indeterminate soft tissue lesion of any size	•New lesion ≥1.0 cm that was absent on initial evaluation • Preexisting lesion: • If <1.0 cm on previous examination, demonstrating >50% growth in long axis on 2 consecutive examinations with ≥5 mm absolute increase • If ≥1.0 cm on previous examination, demonstrating >50% growth in long axis on a single examination	• Imaging should be performed ≥4 wk after surgical resection to allow for resolution of postsurgical inflammation.

Anatomic Location	Initial Evaluation: Findings Warranting Customized Radiologic Workup, Repeat Radiographic Evaluation, or Biopsy Prior to Enrollment	Adjuvant Trial Surveillance: Findings Qualifying as Unequivocal Disease Recurrence	Additional Workshop Discussion Points
Pleural effusion or ascites	No radiologic study can definitively differentiate between benign vs malignant processes. In the absence of coexisting nonmalignant clinical disease, indeterminate fluid should be sampled.	• No radiologic study can definitively differentiate between benign vs malignant processes. In the absence of coexisting nonmalignant clinical disease, indeterminate fluid should be sampled.	• In the absence of coexisting nonmalignant clinical disease, indeterminate pleural and ascitic fluid should have cytologic evaluation, if safe and feasible.
Bone	Indeterminate bone lesion	•New lytic or sclerotic bone lesion that was absent on initial evaluation • Multifocal lesions demonstrating geographic distribution or radiographic and/or metabolic features pathognomonic for metastatic disease	• Osseous metastases commonly demonstrate nonspecific features on CT imaging. In the absence of multifocal stereotypical features of osteolytic or osteoblastic metastases, indeterminate lesions should be further evaluated by radiography, MRI, or nuclear medicine imagining.

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging.

Table 3.

Important Diagnostic Considerations in MIBC and Upper-Tract UC Clinical Trial Design

Diagnostic Modality	Workshop Discussion Points	Comments
Urine test use	• Clinical trials should specify whether urine tests are used for postoperative surveillance and, if so, the specific test and testing interval required. • The 2017 AUA/ASCO/ASTRO/SUO guideline recommends regular voided urine cytologic examination for chemoradiotherapy (grade C), urethral wash cytologic examination for high-risk patients with a retained urethra (expert opinion), and to consider using urine cytologic examination after radial cystectomy for upper-tract cancer detection (expert opinion).[30]	• The level of evidence supporting urine-based screening after radical cystectomy is low.[31] Similarly, after chemoradiotherapy, urine test-based tests can be unreliable owing to changes in the cytologic characteristics of radiation-treated urothelium. • The implications of a false positive urine test result can be high, as it usually results in more imaging and often more surgery (eg, ureteroscopy, urethrectomy).[32]
Augmented endoscopy	• Standard-of-care guidelines for endoscopic surveillance should be followed and defined at the start of the trial.	• Two augmented endoscopy methods appear to have the best evidence of efficacy: (1) hexaminolevulinate (blue-light endoscopy),[33,34] and (2) narrow-band imaging.[35,36] • Clinical trials should standardize or account for how endoscopy is performed since differences in bladder recurrence and progression rates could be potentially attributable to imbalances in the method of surveillance rather than the intervention being tested.
Random bladder biopsies	• Clinical trials should specify whether random bladder biopsies should be obtained or not obtained to rule out occult carcinoma in situ. • It is unclear whether random bladder biopsies should be done for all patients with intact bladders.	• Most low-grade bladder tumors will have normal urine cytologic characteristics but will be visible as a papillary tumor at cystoscopy. • Most high-grade bladder tumors, however, will have positive cytologic characteristics defined as high-grade malignant cells and will be visible as a flat red patch, a papillary tumor, or a nodular/sessile tumor at endoscopy. • Carcinoma in situ may not be visible with standard white light cystoscopy in up to 50% of patients, providing a rationale for mapping biopsies of normal-appearing bladder mucosa. This is especially important for patients with unexplained positive cytologic test results. • It is not clear that the biopsy of normal-appearing bladder urothelium is of any benefit if results of urine cytologic and cystoscopic examination are normal.[37–41]

Abbreviations: ASCO, American Society of Clinical Oncology; ASTRO, American MIBC, muscle-invasive bladder cancer; SUO, Society of Urologic Oncology; Society for Radiation Oncology; AUA, American Urological Association; UC, urothelial carcinoma.