AUA
VOLUME 42 UPDATE SERIES LESSON 12
2023

Adjuvant and Early Salvage Therapy Recommendations Following Radical Surgery in Urological Cancers

Learning Objective: At the conclusion of this continuing medical education activity, the participant will be able to identify risk factors in patients with localized urological cancer who are candidates for adjuvant or salvage therapy, engage with colleagues in multidisciplinary discussions regarding the evidence supporting medical decision-making and treatment in adjuvant or salvage therapy situations, describe the evidence supporting medical decision-making and treatment in adjuvant or early salvage therapy with respect to high-risk prostate cancer following surgery, and identify and engage in multidisciplinary discussions regarding the evidence supporting adjuvant therapy for patients with renal cell and urothelial carcinoma.

This AUA Update aligns with the American Board of Urology Module on Oncology, Urinary Diversion, and Adrenal. Additional information on this topic can be found in the AUA Core Curriculum sections on Oncology-Bladder and Oncology-Prostate.

Scan the QR Code to view author disclosures or visit [https://qrco.de/bdUWos]

Daniel C. Parker, MD,[1] Michael S. Cookson, MD,[1] and Elisabeth I. Heath, MD[2]

[1]Stephenson Oklahoma Cancer Center, The University of Oklahoma College of Medicine, Oklahoma City, Oklahoma

[2]Karmanos Cancer Institute, Wayne State University School of Medicine, Detroit, Michigan

American Urological Association

Accreditation: The American Urological Association (AUA) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Credit Designation: The American Urological Association designates this enduring activity for a maximum of 1.0 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

KEY WORDS: adjuvant therapy, salvage therapy, prostate cancer, bladder cancer, kidney cancer

INTRODUCTION

A frequent challenge faced by urologists when treating patients with prostate, bladder, kidney, and upper tract urothelial cancers is how to properly manage the patient with adverse pathological features following radical surgery. Confounders to the problem include the uncertainty that exists in our understanding of the natural history of some cancers, the inexact science of selecting patients most likely to benefit from aggressive secondary treatments, and considerations to the patient's functional recovery that affect quality of life irrespective of disease control. A better understanding of these issues combined with early identification and timely referral will improve outcomes following surgical intervention.

This Update intends to introduce the past, present, and future of post-surgical therapies pertaining to 4 common adult urological cancers, with an emphasis on primary oncologic outcomes. For the purposes of this Update, adjuvant therapy refers to the delivery of secondary treatments based on high-risk features before clinical evidence of relapse has occurred. Salvage therapy, on the contrary, is defined as therapy provided only to those patients who relapse following a course of definitive primary treatment.

Adjuvant and salvage therapies for these diseases are changing rapidly, so this guidance is intended to be interpreted in the context of contemporary clinical practice guidelines. Multidisciplinary collaboration is the bedrock of successful management of these patients, and we hope that many of the complex decisions fielded by our nonurological colleagues also are illustrated. Ultimately, a better understanding of this rapidly evolving field should raise awareness and improve outcomes among these high-risk patients.

PROSTATE CANCER

The 2019 AUA Guidelines regarding adjuvant and salvage therapy following radical prostatectomy (RP) emphasize 3 key elements that portend an elevated risk of disease relapse. **Positive surgical margins, seminal vesicle invasion, and extraprostatic extension have been associated with treatment failure in key oncologic outcomes such as biochemical recurrence, local and regional recurrence, and progression to metastatic disease.**[1]

Adjuvant radiation. Data from 3 randomized trials comparing adjuvant radiation therapy (ART) with observation following RP comprise the foundation of evidence supporting adjuvant treatment for high-risk individuals: the Southwest Oncology Group (SWOG) Trial 8794,[2] the European Organization for Research and Treatment of Cancer (EORTC) Trial 22911,[3] and the European ARO 96-02 Trial.[4] Notably, each trial enrolled patients under different criteria, evaluated distinct primary end points, and exposed patients to varying doses or modalities of radiotherapy without concurrent androgen deprivation therapy (ADT). Therefore, true meta-analytic consensus for the efficacy of ART on certain oncologic outcomes is lacking, and straightforward extrapolation of the trials' protocols to contemporary practice is not advised. However, all 3 of these trials using ART demonstrated a significant improvement in their primary end points compared with observation (Table 1).

SWOG-8794 randomized 214 patients to ART (60-64 Gy) and compared them with 211 observational patients.[2] Observation, or usual care, was described in the study methodology as biochemical and radiographic surveillance of the patient until an end point event was met. All patients had undergone RP with resultant pathology demonstrating at least 1 high-risk factor. An undetectable PSA was not required for participation. **SWOG-8794 is the only major randomized trial in the ART literature to use metastasis-free survival as a**

Table 1. Phase 3 Adjuvant Radiation Therapy vs Observation Trials for High-risk Prostate Cancer (HR Favors Adjuvant Therapy)

	No. patients	Undetectable PSA required?	Radiation dose (Gy)	Radiation fractions	Androgen deprivation?	Median follow-up (y)	Primary end point	HR for primary end point	HR for overall survival
SWOG-87942	425	No	60-64	30-32	No	12	Metastasis-free survival	0.71 ($P = .016$)	0.72 ($P = .023$)
EORTC-229113	1,005	No	50	25	No	10.6	Biochemical progression-free survival	0.49 ($P < .001$)	1.18 ($P = .202$)
ARO 96-024	388	Yes	60	30	No	9.3	Clinical progression-free survival	0.51 ($P < .001$)	Not reported

Abbreviations: HR, hazard ratio; PSA, prostate-specific antigen.

ABBREVIATIONS: androgen deprivation therapy (ADT), adjuvant radiation therapy (ART), European Organization for Research and Treatment of Cancer (EORTC), hazard ratio (HR), neoadjuvant chemotherapy (NAC), number needed to treat (NNT), programmed death ligand-1 (PDL1), radical prostatectomy (RP), salvage radiation therapy (SRT), Southwest Oncology Group (SWOG), upper tract urothelial carcinoma (UTUC)

primary end point. With more than 10 years of follow-up, 43% of the ART arm had experienced a metastatic event or died of prostate cancer compared with 54% of the observation arm (hazard ratio [HR] 0.71). Median overall survival–a secondary end point of the trial–was improved by nearly 2 years with ART (15.2 years vs 13.3 years, HR 0.72). The number needed to treat (NNT; ie, the number of patients needed to undergo ART to prevent 1 case of progression to metastatic disease) was 12.2. The NNT for the overall survival outcome was 9.1.

EORTC-22911 randomized 1,005 post-prostatectomy patients in 1:1 fashion to either ART (60 Gy) or watchful waiting,[3] but in this trial, the primary end point was biochemical progression-free survival. Biochemical progression was defined as a PSA level higher than 0.2 µg/L on at least 2 occasions. An undetectable PSA was not a component of the inclusion criteria. During a median follow-up period of nearly 11 years, 198 patients in the ART arm experienced biochemical recurrence vs 311 in the observation group (HR 0.49). Overall survival was not significantly affected by adjuvant radiation in EORTC-22911 (HR 1.18, $P = .20$).

A total of 388 patients were enrolled and randomized in ARO 96-02.[4] Another unique end point–clinical progression-free survival–was measured that encompassed not just biochemical recurrence, but radiographic progression and death as well. ARO 96-02 was the only trial to include 3-dimensional conformal radiation delivery technology in its design (60 Gy dose). **Additionally, the inclusion criteria in ARO 96-02 specified that eligible patients must have achieved an undetectable PSA following RP.** With 10 years of median follow-up, there were 61 progression events (41%) in the ART arm vs 100 events (63%) in the observation arm (HR 0.51).

To synthesize the literature for the 2019 AUA Guidelines on the use of ART, panel members performed a pooled analysis of certain primary and secondary end points from the 3 major randomized trials reviewed above.[1] **For example, data on biochemical recurrence were available from all 3 trials, and the guideline panel's pooled analysis demonstrated that ART improves the risk of PSA failure after RP by 53% in high-risk patients. The NNT for biochemical progression in this same meta-analysis was 4.4.** Expanding the analysis for clinical progression-free survival using data combined from SWOG-8794 and EORTC-22911 yielded an NNT of 13.8. Finally, in terms of local or regional disease recurrence after RP, 9.8 patients would require treatment with ART to prevent 1 treatment failure.

Subgroup analyses of patients in the 3 major trials have been performed with the intention of further clarifying which patients stand to benefit the most from ART after RP. Unfortunately, the results of these post hoc studies tend to demonstrate a loss of benefit of ART in the chosen subgroup. For example, patients in EORTC-22911 undergoing ART with negative surgical margins did not achieve an improvement in biochemical-free survival and endured worse overall survival by 68%.[3] The presence of seminal vesical invasion eliminated the biochemical progression-free survival advantage of ART in ARO 96-02.[4] EORTC-22911 demonstrated no improvement in progression or overall survival for the subgroup of patients with extraprostatic extension undergoing ART.[3] In contrast, younger age groups and those with higher Gleason grades tended to benefit from ART after RP more than their counterparts in the 3 major trials.[1-4]

Role of ADT therapy in ART. **Regarding the use of ADT in the ART setting, none of the 3 major ART trials included the use of hormonal therapy. A forthcoming trial, RADICALS-HD, will examine the efficacy of various durations of ADT on patients undergoing either ART or early salvage radiation.**[5] Participants, irrespective of timing of radiation, will undergo 6 months or 24 months of ADT vs none. **Until those results are reported, the AUA Guidelines do not recommend combining ART with hormone deprivation.**[1]

Salvage radiation. Despite Level 1 evidence supporting the use of ART for high-risk patents after RP, retrospective data indicate that its use was declining in the U.S. in the 2000s.[6] This was due, in part, to adverse events in the adjuvant setting, possibility of overtreatment, and a growing interest in the use of early salvage radiation therapy (SRT) for patients who reach biochemical recurrence after surgery. **SRT, as opposed to ART, reduces the potential for overtreating individuals never destined to recur thereby, sparing them unnecessary radiation-induced toxicity.**

A network of 3 international randomized clinical trials with a preplanned meta-analysis produced a paradigm shift in favor of early SRT (Table 2).[5,7-9] The Rituximab in Antineutrophil Cytoplasmic Antibodies-Associated Vasculitis (RAVES) trial,

Table 2. Phase 3 Adjuvant Radiation vs Salvage Radiation Trials for High-risk Prostate Cancer (HR Favors Salvage Radiation Therapy)

	No. patients	Radiation dose (Gy)	Radiation fractions	Androgen deprivation?	Median follow-up (y)	Primary end point	HR for primary end point
RAVES[7]	333	64	32	No	6.1	Biochemical progression-free survival	1.15 ($P = .15$)
RADICALS-RT[a,5]	1,396	66 or 52.5 (nonrandomized)	33 or 20	Yes (24% of ART arm; 27% of SRT arm)	4.9	Biochemical progression-free survival[a]	1.10 ($P = .56$)
GETUG-AFU-17[8]	424	66	33	Yes	6.3	Event-free survival	0.81 ($P = .42$)

Abbreviations: ART, adjuvant radiation therapy; HR, hazard ratio; SRT, salvage radiation therapy.
[a]RADICALS-RT primary end point changed to metastasis-free survival, but only biochemical progression data were mature at initial reporting.

conducted in Australia and New Zealand, tested ART vs SRT after RP in high-risk individuals who demonstrated an initial biochemical remission.[7] ART was defined as radiation delivered within 6 months of surgery, whereas patients randomized to SRT underwent radiation once surpassing a PSA threshold of 0.2 ng/mL. Both arms of the trial received a 64 Gy dose of radiation, and ADT was not used. RAVES was powered as a non-inferiority trial with a primary end point of biochemical progression-free survival. At 6 years of follow-up, no significant difference was found between groups who experienced a biochemical progression, and the SRT group demonstrated improved rates of high-grade urinary and sexual toxicities.

Nearly 1,400 patients were similarly randomized after RP to ART or SRT in RADICALS-RT, which was open across the United Kingdom, Ireland, Denmark, and Canada.[5] An overlapping trial, RADICALS-HD, was carried out simultaneously testing the performance of various durations of ADT on those patients who underwent post-RP radiation. In total, 24% of the ART arm and 27% of the SRT arm received some duration of ADT during their assigned treatment, either due to concomitant enrollment in RADICALS-HD (6 months vs 24 months) or based on the judgment of their treating physician. Patients received doses of either 66 Gy or 52.5 Gy in 33 or 20 fractions, respectively. The primary outcome of the initial trial design, disease-free survival, was changed to metastasis-free survival when it became clear that the trial data would be utilized in the preplanned ARTISTIC meta-analysis. At the time of the first data release in 2020, biochemical progression-free survival rates in RADICALS-RT were statistically similar between the 2 arms (ART 85%, SRT 88%). Data regarding metastasis-free survival and overall survival were not mature enough for reporting at the current median follow-up of 4.9 years. As in RAVES, the rates of patient-reported urinary toxicities were significantly worse for the ART arm.

The GETUG-AFU-17 trial stands out from its counterparts for the incorporation of short-term (6 months) ADT for both ART and SRT arms in the trial design.[8] The prostate radiation dose was 66 Gy. Event-free survival—defined as time to biochemical progression, metastasis, or death—was the primary end point. The study was prematurely closed to accrual due to a paucity of event outcomes. However, analysis of the 424 enrolled patients at the time of study closure demonstrated no significant benefit to ART vs SRT in event-free survival (ART 92%, SRT 90%). Rates of grade 2 or higher urinary and erectile function toxicity were significantly worse for the ART arm.

In 2021, the results of the preplanned meta-analysis of the 3 SRT trials were published.[9] ARTISTIC included data derived from the 3 independent contributing trials on the more than 2,000 men. **Not surprisingly, ARTISTIC confirmed the messaging of RAVES, RADICALS-RT, and GETUG-AFU-17. At a median follow-up of 5 years, there was no statistically significant benefit to ART in event-free survival compared with SRT.** ARTISTIC further examined the timing of post-RP radiation on event-free survival by subgroups that included pre-RP PSA level, surgical margin status, seminal vesicle invasion, and postoperative risk stratification (CAPRA-S). There was no signal for superiority of ART in any of these subgroup analyses.

Role of ADT in SRT. As alluded to in the design of the GETUG-AFU-17 trial, the evidence in support of adding ADT with SRT is more robust than currently exists in the ART setting. In the NRG/RTOG-9601 trial, patients undergoing SRT were assigned to placebo vs 24 months of bicalutamide 150 mg daily.[10] A total of 760 patients were enrolled and deemed eligible for analysis. **The addition of bicalutamide to SRT improved the HR for overall survival by 23%, resulting in an absolute improvement in mortality of 5% between treatment arms. Over 12 years of study follow-up, the rate of prostate cancer–specific death was improved by 7.6% due to bicalutamide.**

A post hoc study of RTOG-9601 validated a proprietary genomic classifier as a predictor of which patients would derive the most benefit from ADT exposure during SRT.[11] Among patients with a PSA level of 0.7 ng/mL or less at the time of starting SRT, the absolute effect of bicalutamide was more pronounced in those patients with a Decipher score in the high-risk stratification than for those in the low-risk category. Although the trial was technically underpowered to predict the direct effect of bicalutamide by the Decipher score, this study was provocative in its assertion that not all men benefit equally from ADT during SRT.

The GETUG-AFU-16 trial examined the use of short-term (6 months) goserelin exposure vs no ADT on biochemical progression-free survival in patients undergoing SRT.[12] **At a median follow-up of 112 months, goserelin exposure improved the risk of biochemical progression by 46%. In absolute terms, 15% more patients in the goserelin arm experienced freedom from biochemical progression compared with the radiotherapy-only arm.**

The lymph node-positive patient. Notably absent from the 2019 AUA Guidelines' list of poor prognostic indicators following RP is pathological lymph node positivity. These patients also are frequently recommended to consider adjuvant or salvage therapy. **Guidelines from the National Comprehensive Cancer Network outline 3 management strategies for patients with N1 disease following RP**; **however, the strength of evidence supporting the options varies in robustness.**[13]

The only positive Level 1 evidence that exists for management of the lymph node–positive patient comes from a 2006 randomized trial of patients exposed to continuous ADT (goserelin or orchiectomy) immediately following RP vs at the time of clinical progression. The Messing trial accrued patients between the years of 1988-1993, which is notable for being prior to the emergence of the PSA test in mainstream prostate cancer surveillance. A total of 47 node-positive patients were randomized to ADT, whereas 51 underwent postoperative observation. Seven patients in the ADT arm died during the 12-year follow-up period compared with 25 in the observation arm, which corresponded to an 84% improvement in overall survival. Improved rates of clinical progression-free survival and prostate cancer-specific survival also favored the ADT arm.

Lymph node–positive patients are a heterogeneous group, however, and retrospective evidence quickly amassed suggesting that not all patients in this situation are still affected by lethal disease after surgery alone. In the most contemporary of these series, nearly one-third of 369 lymph node–positive patients achieved a biochemical recurrence-free state as far as 10 years out from surgery with observation.[14] The National Comprehensive Cancer Network includes observation as an

option for these patients, with the caveat that treatment should be considered at the time of a detectable PSA based on extrapolated logic from the more recent SRT data presented above.

Adjuvant external beam radiation coupled with ADT is a third option for the lymph node–positive patient based on category 2 evidence. Da Pozzo et al performed a retrospective review of 250 N1 patients between 1988 and 2002.[15] In their multivariable regression models, only receipt of ART and number of positive lymph nodes were predictors of biochemical recurrence-free survival and cancer-specific survival. Similar series have suggested an impact on all-cause mortality as well.[16,17] Finally, the use of ADT in combination with ART in the lymph node–positive setting is indirectly bolstered by evidence from a single study of the National Cancer Database showing that combination therapy improved mortality rates in patients with clinical node positivity prior to upfront radiation.[18]

More recent attempts to increase options for adjuvant treatment of the N1 patient have not been successful. The Scandinavian Prostate Cancer Group 12 trial, released in 2018, randomized 459 high-risk or N1 patients after prostatectomy to receive adjuvant docetaxel for 6 cycles vs observation.[19] Unfortunately, docetaxel only improved biochemical recurrence-free survival by a statistically insignificant 3.2 months. Therefore, docetaxel is not a guideline-concordant strategy for adjuvant therapy in prostate cancer after prostatectomy.

BLADDER CANCER

Since 1999, the use of systemic therapy in the perioperative management of patients with muscle-invasive bladder cancer has been mostly focused on the neoadjuvant setting. Two international trials of neoadjuvant chemotherapy (NAC) vs upfront radical cystectomy ultimately led to cisplatin-based NAC becoming standard of care.[20,21] The earliest and largest of these trials demonstrated an absolute improvement in 3-year overall survival of 5.5% for patients who received neoadjuvant cisplatin, methotrexate, and vinblastine, which corresponded with 6.5 months of additional survival for those patients.[20]

The primary role of adjuvant chemotherapy in contemporary management of muscle-invasive bladder cancer, according to the AUA Guidelines,[22] is to provide patients, who were not candidates to receive this treatment prior to surgery, with exposure to the benefits of systemic perioperative treatment. These situations are frequently encountered in clinical practice. Cisplatin eligibility can be precluded because of preexisting renal insufficiency, hearing loss, neuropathy, and poor performance status, among other reasons.[23] In circumstances where chemotherapy eligibility of the patient improves after cystectomy, the AUA Guidelines recommend that adjuvant cisplatin-based chemotherapy should be offered.[22]

The true benefit of adjuvant chemotherapy has been historically difficult to demonstrate. Of the available trials testing the efficacy of adjuvant chemotherapy, many are now quite dated and use chemotherapy regimens that are no longer considered standard.[24,25] Larger, more contemporary randomized trials, such as EORTC-30994, failed to meet accrual goals, leading to negative overall survival findings.[26,27] Two meta-analyses of the available trial data indicate that an overall survival benefit may, in fact, exist for adjuvant chemotherapy in the range of a 23%-25% improvement in the risk of death.[28,29] These meta-analyses are criticized in the AUA Guidelines, however, for pooling a composite of heterogeneous trial data that were underpowered to study their primary outcomes in the first place.[22]

In 2021, the results of 2 major trials examining the efficacy of immune checkpoint inhibition on outcomes in the adjuvant bladder cancer setting were published. **Checkmate-274 studied whether the programmed death ligand-1 (PDL1) monoclonal antibody nivolumab could affect disease-free survival (Figure 1).[30]** Following radical cystectomy, patients

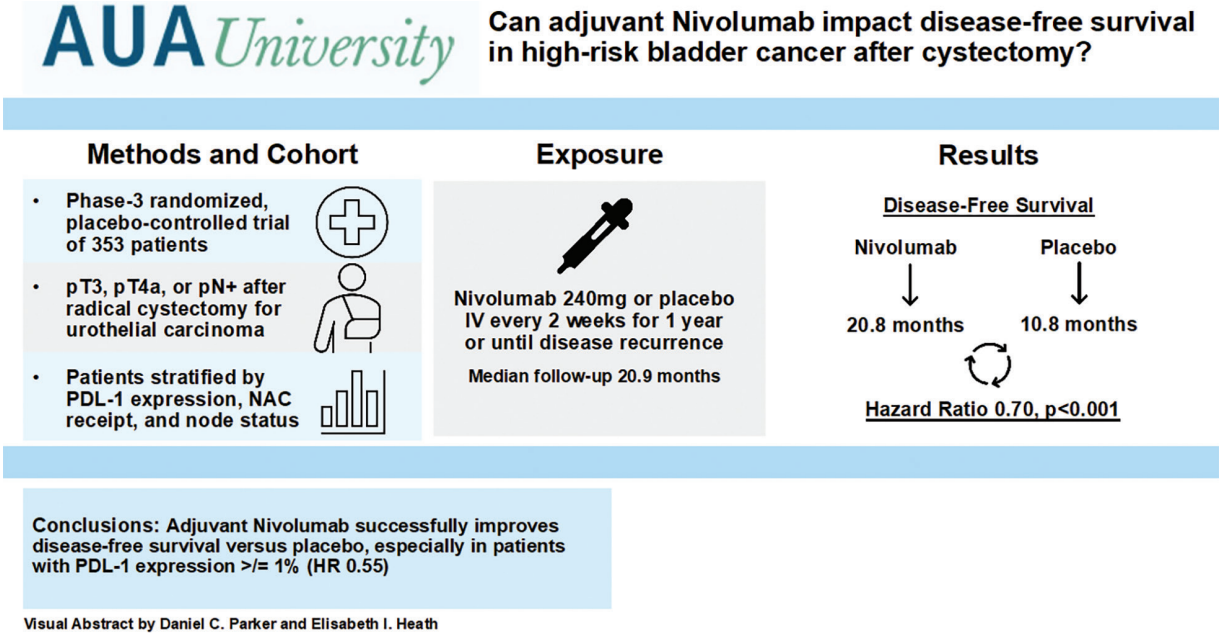

Figure 1. Visual abstract of the Checkmate-274 Trial. HR indicates hazard ratio; IV, intravenous; NAC, neoadjuvant chemotherapy.[30] Reprinted with permission from AUA*University*.

were randomized in 1:1 fashion to receive either a 240 mg infusion of nivolumab twice per month for 1 year or placebo. Outcomes were stratified based on the level of host tumor expression of PDL1 (greater or less than 1%). About 43% of each arm reported prior receipt of NAC. **With more than 20 months of follow-up for each arm, adjuvant nivolumab improved the risk of disease recurrence after cystectomy or death by 30%. This effect was even more pronounced among patients with ligand expression greater than or equal to 1% in whom disease-free survival and death were improved by 45%.** Based on these results, adjuvant nivolumab is now considered an option for adjuvant therapy following cystectomy independent of NAC status.

Not all immunotherapies appear to have utility as adjuvant therapy in muscle-invasive bladder cancer, however. The IMVIGOR010 trial, also released in 2021, randomized patients to observation vs up to 1 year of atezolizumab exposure.[31] Atezolizumab only improved disease-free survival by 2.8 months, which failed to reach statistical significance or justify the 16% rate of high-grade adverse events in the treatment arm. Nivolumab is now being studied as an adjuvant therapy in patients with muscle-invasive bladder cancer following combined chemotherapy and radiation as primary treatment (NCT03171025). Several additional trials of adjuvant therapy following radical cystectomy are ongoing in the United States (Table 3).

KIDNEY CANCER

Early diagnosis and treatment of localized renal cell carcinoma leads to freedom from disease recurrence at 5 years for more than 90% of affected patients.[32] Some series with follow-up exceeding 10 years, however, suggest that regional and distant relapse rates may approach 20%.[33] **Pathological stage continues to be the most important prognostic indicator for identifying patients who may not be cured with upfront surgery alone, but other factors (eg, grade, presence of necrosis, sarcomatoid features, lymph node status) have been incorporated consistently as high-risk features in contemporary predictive nomograms.[34-36]** Recently, attention has focused on using biomarker signatures to create predictive molecular assays that have yet to achieve widespread adoption, primarily due to lack of validation and cost.[37,38]

The recent history of adjuvant therapy in localized kidney cancer has been fraught with negative clinical trials.[39] Independent studies of first-generation immunotherapy agents failed to demonstrate a survival benefit with adjuvant interferon-α,[40,41] interleukin-2,[42] or a combination of both.[43] Monoclonal antibody therapy[44] and antitumor vaccines[45] have similarly underperformed in the adjuvant setting. Initial randomized trials testing the use of various tyrosine kinase inhibitors and targeted therapies against the mTOR pathway in adjuvant kidney cancer all reported disappointing results.[39]

S-TRAC was a randomized placebo-controlled trial of sunitinib that came closest to providing a rationale for administering tyrosine kinase inhibitors in the adjuvant setting.[46] High-risk patients who were deemed eligible for inclusion had clear cell histology and at least T3 disease with or without evidence of pathological lymph node metastasis. The primary outcome measured was disease-free survival. At the time of the trial's initial publication, adjuvant sunitinib improved disease-free survival by 1.2 years compared with placebo (HR 0.76). Disappointingly, the final report 2 years later indicated no improvement in overall survival with the addition of adjuvant sunitinib, although its effect on disease-free survival was sustained across subgroups that contained even the patients of the highest risk.[47] With nearly two-thirds of patients in the initial report experiencing high-grade adverse events and no overall survival benefit to justify the risks, S-TRAC failed to generate enthusiasm for routine use in adjuvant renal cell carcinoma.

A similar story may be in the telling for immune checkpoint inhibitors as adjuvant therapy in kidney cancer. **The**

Table 3. Ongoing U.S. Clinical Trials in Muscle-invasive Bladder Cancer for High-risk Patients Following Radical Cystectomy

ClinicalTrials.gov identifier	Estimated enrollment	Intervention	Comparator	Key inclusion criteria	Primary end point
IMVIGOR010[a] (NCT04660344)	495	Atezolizuma[b]	Placebo	• ctDNA-positive • PDL1-positive	Disease-free survival
GETUG-AFU-30[c] (NCT03333356)	109	Pelvic radiotherapy (50 Gy, 38 fractions)	Surveillance	• Negative surgical margins	Pelvic recurrence-free survival
PROOF-302[a] (NCT04197986)	218	Infigratinib[d]	Placebo	• Status post-radical nephroureterectomy, distal ureterectomy, or radical cystectomy • FGFR3 mutation-positive	Disease-free survival
AMBASSADOR[a] (NCT03244384)	739	Pembrolizumab	Observation	• Bladder or upper tract allowed • Variant histology allowed if urothelial is predominant	Overall and disease-free survival

Abbreviations: ctDNA, circulating tumor DNA; FGFR, fibroblast growth factor receptor; PDL1, programmed death ligand-1.
[a]Denotes phase 3 trial.
[b]Atezolizumab is a monoclonal antibody against PDL-1.
[c]Denotes phase 2 trial.
[d]Infigratinib is an oral targeted FGFR1-3 inhibitor.

Keynote-564 trial, released in 2021, randomized 967 patients after radical nephrectomy to either receive placebo or pembrolizumab, a monoclonal antibody against PDL1 (Figure 2).[48] At the time of the interim results report (24 months of follow-up), adjuvant pembrolizumab was associated with a 9.2% absolute improvement in disease-free survival (HR 0.68). Although the preliminary HR for death (HR 0.54) was a promising indicator, the overall survival data were immature for reporting. Therefore, it remains to be seen whether history, as written by S-TRAC, will repeat itself. A robust overall survival benefit will be necessary for widespread adoption of pembrolizumab in adjuvant treatment since concerns regarding its cost, safety, and appropriateness as an adjuvant monotherapy have already been raised.[49]

Three forthcoming trials will continue to explore the effects of immunotherapy on outcomes for high-risk patients with localized kidney cancer (Table 4). The PROSPER trial (NCT03055013) is exploring neoadjuvant and adjuvant nivolumab vs observation. IMmotion (NCT03024996) utilizes atezolizumab as adjuvant monotherapy vs placebo. RAMPART (NCT03288532) is a multiarm trial examining observation vs either adjuvant single agent durvalumab or combination durvalumab with tremelimumab.

UPPER TRACT UROTHELIAL CANCER

Upper tract urothelial carcinoma (UTUC) is the least frequently encountered of the malignancies in this Update, affecting around 3,000 patients in the United States each year. UTUC, compared with the other urological cancers, also has one of the most dismal disease-free survival rates following radical surgery, perhaps as poor as 61%. Recent studies have suggested that more than half of patients undergoing radical nephroureterectomy will demonstrate at least muscle-invasive disease or lymph node invasion on final pathology. The majority of patients who relapse after nephroureterectomy will die from UTUC in less than 3 years.[50]

These prognoses are a testament to how difficult this cancer can be to accurately stage preoperatively and are reflective of UTUC's aggressive biology. As a result, the role of systemic therapy in the management of localized UTUC makes the most sense in the neoadjuvant setting, where the goals of treatment are to improve the likelihood that surgery is truly consolidative.

Other arguments for preferring neoadjuvant use of chemotherapy over adjuvant approaches in UTUC are rational as well. Since performance of radical nephroureterectomy, by definition, leads to the loss of an entire renal unit, opportunities for patients to receive adjuvant chemotherapy are commonly lost to renal function attrition or declines in performance status postoperatively. Unfortunately, a prospective phase 3 randomized trial involving NAC in UTUC is lacking, and so the strongest level of evidence still supports the application of chemotherapy in adjuvant settings for appropriately selected patients.

The POUT trial randomized high-risk patients following nephroureterectomy to observation vs 4 months of adjuvant chemotherapy (Figure 3).[51] High-risk patients were those with tumor stages greater than or equal to pT2, evidence of lymph node invasion, or both. Chemotherapy regimens commenced within 90 days of surgery and included either cisplatin plus gemcitabine or carboplatin plus gemcitabine, depending on renal function criteria. The primary end point of the study was disease-free survival. A total of 261 patients were enrolled over the 5-year study period across institutions in the United Kingdom. **At a median follow-up of about 2.5 years, adjuvant chemotherapy improved the HR for disease-free survival by 55%, corresponding to a 25% absolute improvement in the event rate between treatment arms.** Based on the results of the POUT trial and absence of corresponding Level 1 evidence in the neoadjuvant space, adjuvant platinum-containing chemotherapy after radical nephroureterectomy should be at least a consideration

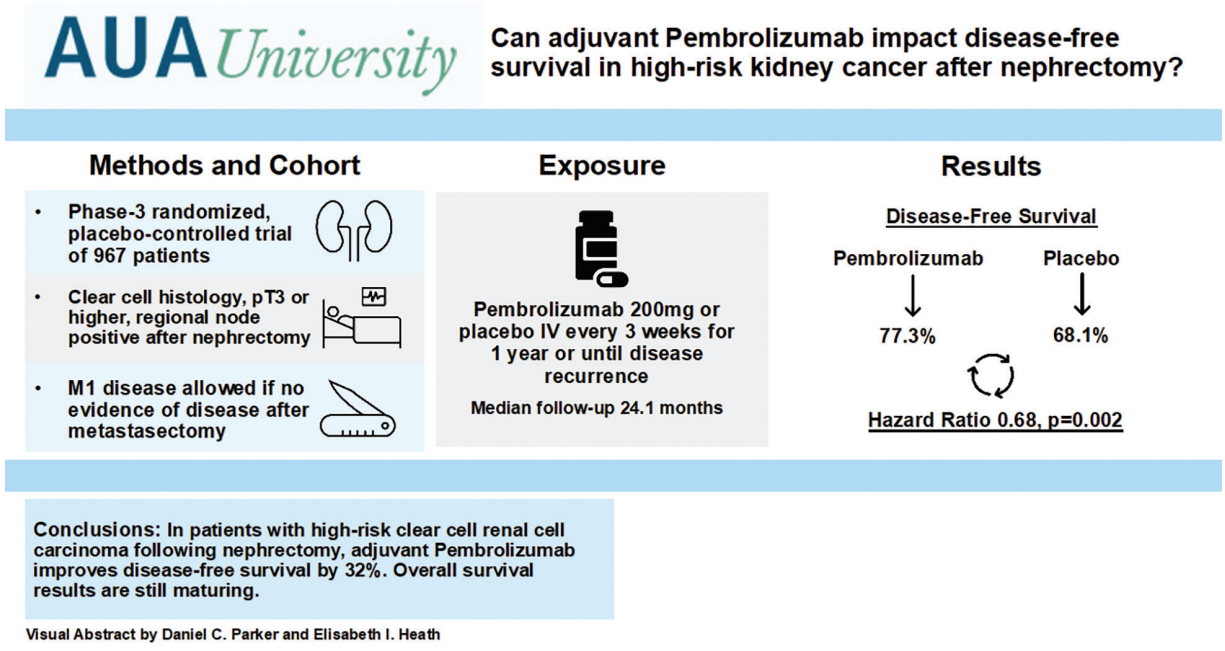

Figure 2. Visual abstract of the Keynote-564 trial. IV indicates intravenous.[48] Reprinted with permission from AUA*University*.

Table 4. Ongoing U.S. Clinical Trials in Renal Cell Carcinoma for High-risk Patients Following Radical Nephrectomy or Partial Nephrectomy

ClinicalTrials.gov identifier	Estimated enrollment	Intervention	Comparator	Key inclusion criteria	Primary end point
IMMOTION-010[a] (NCT03024996)	778	Atezolizumab	Placebo	• Clear cell or sarcomatoid histology • Radical or partial nephrectomy	Disease-free survival
CHECKMATE-914[a] (NCT03138512)	1,600	Nivolumab or nivolumab + ipilimumab[b]	Placebo	• Clear cell histology • Radical or partial nephrectomy	Disease-free survival
PROSPER[a] (NCT03055013)	766	Neoadjuvant and adjuvant nivolumab	Observation	• cT2Nx or TanyN+ • Must have a renal mass biopsy • Any RCC histology • Fewer than 3 masses	Event-free survival
RAMPART[a] (NCT03288532)	1,750	Durvalumab or durvalumab[c] + tremelimumab[d]	Active monitoring	• All RCC subtypes eligible	Overall and disease-free survival

Abbreviation: RCC, renal cell carcinoma.
[a]Denotes phase 3 trial.
[b]Ipilimumab is a monoclonal antibody against CTLA4.
[c]Durvalumab is an anti-programmed death ligand-1 antibody.
[d]Tremelimumab is a monoclonal antibody against CTLA4.

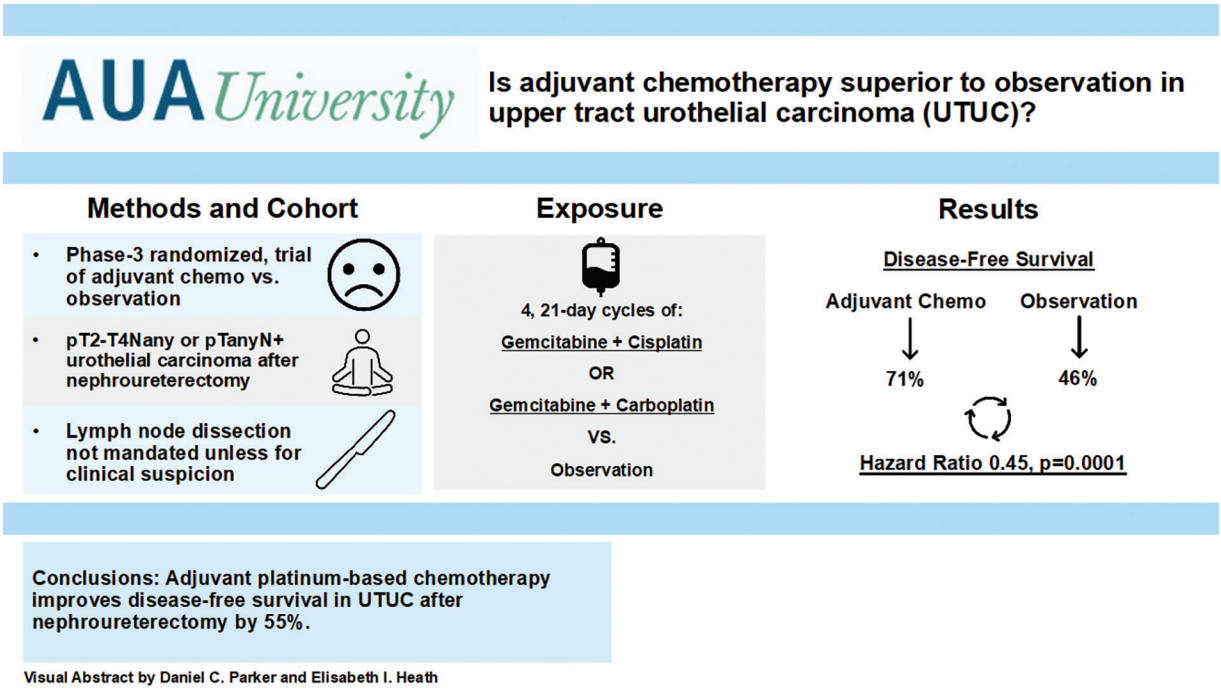

Figure 3. Visual abstract of the POUT trial. Chemo indicates chemotherapy.[51] Reprinted with permission from AUA*University*.

for all patients. However, NAC can instead be offered in particularly high-risk situations based on a lower category of evidence or preferably within the context of a clinical trial.[50]

Lastly, consideration must be given to prevention of relapses of urothelial carcinoma within the urinary bladder following radical nephroureterectomy. Currently, data from 2 randomized trials[52,53] and 1 retrospective review[54] support the use of a single intraoperative or postoperative dose of intravesical chemotherapy to prevent bladder recurrences. In the United States, this usually entails administration of mitomycin-C or gemcitabine. No randomized data exist that determine the optimal timing of intravesical chemotherapy administration, but protocols in the available

literature obtained their results by delivering therapy prior to catheter removal.

CONCLUSIONS

Adjuvant and salvage therapies in the most common adult urological malignancies are rapidly changing. Additionally, as our understanding of tumor genetics evolves, the individualized approaches for high-risk situations will become more nuanced. Over the next decade, the results of numerous ongoing clinical trials across the spectrum of urological cancers will continue to drive changes to guideline recommendations. For now, high-risk patients facing complex decisions following surgical treatment of localized prostate, bladder, kidney, and upper tract cancers should all be recommended to consider the established management strategies reviewed in this Update or clinical trial enrollment. A close multidisciplinary relationship among urologists, medical oncologists, radiation oncologists, and clinical trialists remains paramount to ensuring that patients are offered the most up-to-date care and given the best opportunity for improved outcomes following surgery.

DID YOU KNOW?

- Positive surgical margins, seminal vesicle invasion, and extraprostatic extension are all high-risk factors for prostate cancer relapse following RP.
- The results from the RAVES, RADICALS-RT, and GETUG-AFU-17 trials indicate that early salvage radiation therapy is non-inferior to adjuvant radiation for postsurgical treatment of high-risk prostate cancer.
- Adjuvant immunotherapy with nivolumab following radical cystectomy can be considered irrespective of prior chemotherapy status, especially in patients with programmed death ligand-1 expression greater than or equal to 1%.
- Sunitinib and pembrolizumab are both options for adjuvant therapy following radical nephrectomy for renal cell carcinoma based on disease-free survival outcomes.
- Level-1 evidence supports the use of adjuvant cisplatin-based chemotherapy for patients with high-risk upper tract urothelial carcinoma.

REFERENCES

1. Pisansky TM, Thompson IM, Valicenti RK, et al. Adjuvant and salvage radiotherapy after prostatectomy: ASTRO/AUA Guideline Amendment 2018-2019. *J Urol.* 2019;202(3):533-538.
2. Thompson IM, Tangen CM, Paradelo J, et al. Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term follow-up of a randomized clinical trial. *J Urol.* 2009;181(3):956-962.
3. Bolla M, van Poppel H, Tombal B, et al. Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911). *Lancet.* 2012;380(9858):2018-2027.
4. Wiegel T, Bartkowiak D, Bottke D, et al. Adjuvant radiotherapy versus wait-and-see after radical prostatectomy: 10-year follow-up of the ARO 96-02/AUO AP 09/95 trial. *Eur Urol.* 2014;66(2):243-250.
5. Parker CC, Clarke NW, Cook AD, et al. Timing of radiotherapy after radical prostatectomy (RADICALS-RT): a randomised, controlled phase 3 trial. *Lancet.* 2020;396(10260):1413-1421.
6. Sineshaw HM, Gray PJ, Efstathiou JA, Jemal A. Declining use of radiotherapy for adverse features after radical prostatectomy: results from the National Cancer Data Base. *Eur Urol.* 2015;68(5):768-774.
7. Kneebone A, Fraser-Browne C, Duchesne GM, et al. Adjuvant radiotherapy versus early salvage radiotherapy following radical prostatectomy (TROG 08.03/ANZUP RAVES): a randomised, controlled, phase 3, non-inferiority trial. *Lancet Oncol.* 2020;21(10):1331-1340.
8. Sargos P, Chabaud S, Latorzeff I, et al. Adjuvant radiotherapy versus early salvage radiotherapy plus short-term androgen deprivation therapy in men with localised prostate cancer after radical prostatectomy (GETUG-AFU 17): a randomised, phase 3 trial. *Lancet Oncol.* 2020;21(10):1341-1352.
9. Vale CL, Fisher D, Kneebone A, et al; ARTISTIC Meta-analysis Group. Adjuvant or early salvage radiotherapy for the treatment of localised and locally advanced prostate cancer: a prospectively planned systematic review and meta-analysis of aggregate data. *Lancet.* 2020;396(10260):1422-1431.
10. Shipley WU, Seiferheld W, Lukka HR, et al; NRG Oncology RTOG. Radiation with or without antiandrogen therapy in recurrent prostate cancer. *N Eng J Med.* 2017;376(5):417-428.
11. Feng FY, Huang H-C, Spratt DE, et al. Validation of a 22-gene genomic classifier in patients with recurrent prostate cancer. *JAMA Oncol.* 2021;7(4):544-552.
12. Carrie C, Magné N, Burban-Provost P, et al. Short-term androgen deprivation therapy combined with radiotherapy as salvage treatment after radical prostatectomy for prostate cancer (GETUG-AFU 16): a 112-month follow-up of a phase 3, randomised trial. *Lancet Oncol.* 2019;20(12):1740-1749.
13. Schaeffer E, Srinivas S, Antonarakis ES, et al. NCCN Guidelines insights: prostate cancer, version 1.2021: featured updates to the NCCN Guidelines. *J Natl Compr Canc Netw.* 2021;19(2):134-143.
14. Touijer KA, Mazzola CR, Sjoberg DD, et al. Long-term outcomes of patients with lymph node metastasis treated with radical prostatectomy without adjuvant androgen-deprivation therapy. *Eur Urol.* 2014;65(1):20-25.
15. Da Pozzo LF, Cozzarini C, Briganti A, et al. Long-term follow-up of patients with prostate cancer and nodal metastases treated by pelvic lymphadenectomy and radical prostatectomy: the positive impact of adjuvant radiotherapy. *Eur Urol.* 2009;55(5):1003-1011.
16. Abdollah F, Karnes RJ, Suardi N, et al. Impact of adjuvant radiotherapy on survival of patients with node-positive prostate cancer. *J Clin Oncol.* 2014;32(35):3939-3947.
17. Briganti A, Karnes RJ, Pozzo LFD, et al. Combination of adjuvant hormonal and radiation therapy significantly prolongs

survival of patients with pT2–4 pN+ prostate cancer: results of a matched analysis. *Eur Urol.* 2011;59(5):832-840.

18. Lin CC, Gray PJ, Jemal A, Efstathiou JA. Androgen deprivation with or without radiation therapy for clinically node-positive prostate cancer. *J Natl Cancer Inst.* 2015;107(7):djv119.
19. Ahlgren GM, Flodgren P, Tammela TLJ, et al. Docetaxel versus surveillance after radical prostatectomy for high-risk prostate cancer: results from the prospective randomised, open-label phase 3 Scandinavian Prostate Cancer Group 12 trial. *Eur Urol.* 2018;73(6):870-876.
20. Neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: a randomised controlled trial. International collaboration of trialists. *Lancet Lond Engl.* 1999;354(9178):533-540.
21. International Collaboration of Trialists; Medical Research Council Advanced Bladder Cancer Working Party (now the National Cancer Research Institute Bladder Cancer Clinical Studies Group); European Organisation for Research and Treatment of Cancer Genito-Urinary Tract Cancer Group. International phase III trial assessing neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: long-term results of the BA06 30894 trial. *J Clin Oncol.* 2011;29(16):2171-2177.
22. Chang SS, Bochner BH, Chou R, et al. Treatment of non-metastatic muscle-invasive bladder cancer: AUA/ASCO/ASTRO/SUO guideline. *J Urol.* 2017;198(3):552-559.
23. Galsky MD, Hahn NM, Rosenberg J, et al. A consensus definition of patients with metastatic urothelial carcinoma who are unfit for cisplatin-based chemotherapy. *Lancet Oncol.* 2011;12(3):211-214.
24. Freiha F, Reese J, Torti FM. A randomized trial of radical cystectomy versus radical cystectomy plus cisplatin, vinblastine and methotrexate chemotherapy for muscle invasive bladder cancer. *J Urol.* 1996;155(2):495-500.
25. Skinner DG, Daniels JR, Russell CA, et al. The role of adjuvant chemotherapy following cystectomy for invasive bladder cancer: a prospective comparative trial. *J Urol.* 1991;145(3):459-464.
26. Cognetti F, Ruggeri EM, Felici A, et al. Adjuvant chemotherapy with cisplatin and gemcitabine versus chemotherapy at relapse in patients with muscle-invasive bladder cancer submitted to radical cystectomy: an Italian, multicenter, randomized phase III trial. *Ann Oncol.* 2012;23(3):695-700.
27. Sternberg CN, Skoneczna I, Kerst JM, et al. Immediate versus deferred chemotherapy after radical cystectomy in patients with pT3–pT4 or N+ M0 urothelial carcinoma of the bladder (EORTC 30994): an intergroup, open-label, randomised phase 3 trial. *Lancet Oncol.* 2015;16(1):76-86.
28. Leow JJ, Martin-Doyle W, Rajagopal PS, et al. Adjuvant chemotherapy for invasive bladder cancer: a 2013 updated systematic review and meta-analysis of randomized trials. *Eur Urol.* 2014;66(1):42-54.
29. Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. Adjuvant chemotherapy for invasive bladder cancer (individual patient data). *Cochrane Database Syst Rev.* 2006;2006(2):CD006018.
30. Bajorin DF, Witjes JA, Gschwend JE, et al. Adjuvant nivolumab versus placebo in muscle-invasive urothelial carcinoma. *N Engl J Med.* 2021;384(22):2102-2114.
31. Bellmunt J, Hussain M, Gschwend JE, et al. Adjuvant atezolizumab versus observation in muscle-invasive urothelial carcinoma (IMvigor010): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol.* 2021;22(4):525-537.
32. Hollingsworth JM, Miller DC, Daignault S, et al. Five-year survival after surgical treatment for kidney cancer: a population-based competing risk analysis. *Cancer.* 2007;109(9):1763-1768.
33. Kim SP, Weight CJ, Leibovich BC, et al. Outcomes and clinicopathologic variables associated with late recurrence after nephrectomy for localized renal cell carcinoma. *Urology.* 2011;78(5):1101-1106.
34. Correa AF, Jegede OA, Haas NB, et al. Predicting disease recurrence, early progression, and overall survival following surgical resection for high-risk localized and locally advanced renal cell carcinoma. *Eur Urol.* 2021;80(1):20-31.
35. Leibovich BC, Blute ML, Cheville JC, et al. Prediction of progression after radical nephrectomy for patients with clear cell renal cell carcinoma. *Cancer.* 2003;97(7):1663-1671.
36. Thompson RH, Leibovich BC, Lohse CM, et al. Dynamic outcome prediction in patients with clear cell renal cell carcinoma treated with radical nephrectomy: the D-SSIGN score. *J Urol.* 2007;177(2):477-480.
37. Rini B, Goddard A, Knezevic D, et al. A 16-gene assay to predict recurrence after surgery in localised renal cell carcinoma: development and validation studies. *Lancet Oncol.* 2015;16(6):676-685.
38. Klatte T, Seligson DB, LaRochelle J, et al. Molecular signatures of localized clear cell renal cell carcinoma to predict disease-free survival after nephrectomy. *Cancer Epidemiol. Biomarkers Prev.* 2009;18(3):894-900.
39. Lenis AT, Donin NM, Johnson DC, et al. Adjuvant therapy for high risk localized kidney cancer: emerging evidence and future clinical trials. *J Urol.* 2018;199(1):43-52.
40. Pizzocaro G, Piva L, Colavita M, et al. Interferon adjuvant to radical nephrectomy in Robson stages II and III renal cell carcinoma: a multicentric randomized study. *J Clin Oncol.* 2001;19(2):425-431.
41. Messing EM, Manola J, Wilding G, et al. Phase III study of interferon alfa-NL as adjuvant treatment for resectable renal cell carcinoma: an Eastern Cooperative Oncology Group/Intergroup trial. *J Clin Oncol.* 2003;21(7):1214-1222.
42. Clark JI, Atkins MB, Urba WJ, et al. Adjuvant high-dose bolus interleukin-2 for patients with high-risk renal cell carcinoma: a cytokine working group randomized trial. *J Clin Oncol.* 2003;21(16):3133-3140.
43. Passalacqua R, Caminiti C, Buti S, et al. Adjuvant low-dose interleukin-2 (IL-2) plus interferon-α (IFN-α) in operable renal cell carcinoma (RCC). *J Immunother.* 2014;37(9):440-447.
44. Chamie K, Donin NM, Klöpfer P, et al. Adjuvant weekly girentuximab following nephrectomy for high-risk renal cell carcinoma: the ARISER randomized clinical trial. *JAMA Oncol.* 2017;3(7):913-920.
45. Wood C, Srivastava P, Bukowski R, et al. An adjuvant autologous therapeutic vaccine (HSPPC-96; vitespen) versus observation alone for patients at high risk of recurrence after nephrectomy for renal cell carcinoma: a multicentre, open-label, randomised phase III trial. *Lancet.* 2008;372(9633):145-154.
46. Ravaud A, Motzer RJ, Pandha HS, et al. Adjuvant sunitinib in high-risk renal-cell carcinoma after nephrectomy. *N Engl J Med.* 2016;375(23):2246-2254.

47. Motzer RJ, Ravaud A, Patard J-J, et al. Adjuvant sunitinib for high-risk renal cell carcinoma after nephrectomy: subgroup analyses and updated overall survival results. *Eur Urol.* 2018;73(1):62-68.

48. Choueiri TK, Tomczak P, Park SH, et al. Adjuvant pembrolizumab after nephrectomy in renal-cell carcinoma. *N Engl J Med.* 2021;385(8):683-694.

49. Magee DE, Kutikov A. Re: Adjuvant pembrolizumab after nephrectomy in renal-cell carcinoma. *Eur Urol.* 2021;81(3):317-318.

50. Kaag MG. Perioperative chemotherapy in the management of high risk upper tract urothelial cancers. *Transl Androl Urol.* 2020;9(4):1881-1890.

51. Birtle A, Johnson M, Chester J, et al. Adjuvant chemotherapy in upper tract urothelial carcinoma (the POUT trial): a phase 3, open-label, randomised controlled trial. *Lancet Lond Engl.* 2020;395(10232):1268-1277.

52. Ito A, Shintaku I, Satoh M, et al. Prospective randomized phase II trial of a single early intravesical instillation of pirarubicin (THP) in the prevention of bladder recurrence after nephroureterectomy for upper urinary tract urothelial carcinoma: the THP monotherapy study group trial. *J Clin Oncol.* 2013;31(11):1422-1427.

53. O'Brien T, Ray E, Singh R, et al. Prevention of bladder tumours after nephroureterectomy for primary upper urinary tract urothelial carcinoma: a prospective, multicentre, randomised clinical trial of a single postoperative intravesical dose of mitomycin c (the ODMIT-C Trial). *Eur Urol.* 2011; 60(4):703-710.

54. Freifeld Y, Ghandour R, Singla N, et al. Intraoperative prophylactic intravesical chemotherapy to reduce bladder recurrence following radical nephroureterectomy. *Urol Oncol.* 2020;38(9):737.e11-737.e16.

Study Questions Volume 42 Lesson 12

1. A 62-year-old man undergoes a radical prostatectomy for clinically localized prostate cancer. His final pathology demonstrates prostatic adenocarcinoma, Gleason grade 4 + 4, with seminal vesicle invasion, a positive margin at the apex, and cancer detected in a single pelvic lymph node. According to the AUA Guidelines, what features of the patient's pathology report warrant consideration for adjuvant radiation therapy?
   a. Gleason grade, seminal vesicle invasion
   b. Seminal vesicle invasion, positive margin
   c. Positive margin, pelvic lymph node involvement
   d. Gleason grade, pelvic lymph node involvement

2. A 66-year-old man undergoes radical prostatectomy with resultant pathology demonstrating focal extracapsular extension but no lymph node metastasis or positive margins. After counseling him to consider adjuvant radiation therapy, he asks you to explain (based on your knowledge of the evidence) how his prognosis would be affected by initial observation and early salvage radiation. You tell him, observation and early salvage radiation therapy have been demonstrated to provide
   a. Inferior oncologic and functional outcomes compared with adjuvant radiation.
   b. Non-inferior oncologic and functional outcomes compared with adjuvant radiation
   c. Non-inferior oncologic outcomes, but superior functional outcomes, compared with adjuvant radiation
   d. Superior oncologic and functional outcomes compared with adjuvant radiation

3. You are having a discussion with a multidisciplinary colleague about a mutual patient. The patient is a 67-year-old man with muscle-invasive bladder cancer, clinically localized. Your colleague argues the patient should proceed directly to radical cystectomy because the absolute benefit of neoadjuvant chemotherapy is small and adjuvant chemotherapy trials have proven to have good oncologic efficacy. Your response, based on the AUA Guidelines, should be to
   a. Agree, citing randomized trial data demonstrating a definite overall survival benefit to adjuvant chemotherapy
   b. Agree, citing the results of 2 meta-analyses demonstrating an overall survival benefit of 50% with adjuvant chemotherapy
   c. Disagree, citing randomized trial data demonstrating no overall survival benefit to neoadjuvant chemotherapy
   d. Disagree, citing 2 meta-analyses composed of underpowered trial data insufficient for demonstrating a definite benefit to adjuvant chemotherapy

4. A 58-year-old man presents to your office 3 months status post-radical cystectomy with neobladder urinary diversion. Preoperatively, he was deemed ineligible for neoadjuvant chemotherapy due to poor baseline hearing loss. After recovering from his cystectomy, his kidney function improved. Final pathology demonstrated T3b N0 disease, and molecular sequencing of the patient's tumor demonstrates PDL1 expression at 2.3%. The most compelling clinical feature for administering adjuvant nivolumab in this case is
   a. PDL1 expression greater than 1%
   b. Chemotherapy-naïve status
   c. pT3b stage
   d. Negative lymph nodes at the time of cystectomy

5. A 71-year-old male presents 2 weeks status post-right radical nephrectomy. Pathology demonstrates an 8-cm clear cell renal cell carcinoma with renal sinus fat invasion. The patient has heard about immune checkpoint inhibitors and wonders whether Food and Drug Administration–approved options are available for him. Based on the available data, you recommend
   a. Atezolizumab
   b. Ipilimumab
   c. Nivolumab
   d. Pembrolizumab