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REVIEW ARTICLE

Urothelial carcinoma: Perioperative considerations from top to bottom

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Abstract

Urothelial carcinoma is an aggressive entity that is associated with significant morbidity, but there have been major advances in both our understanding of and treatment options for patients with this disease. In this review, the authors focus on novel therapeutic and diagnostic approaches in the perioperative setting, with an emphasis on patient-centered and individualized care. For urothelial carcinoma of the bladder (UCB), advances in nonplatinum-based therapies, specifically immunotherapy and antibody–drug conjugates, have expanded the therapeutic arsenal for patients with muscle-invasive UCB in both the neoadjuvant and adjuvant settings to improve survival outcomes. Given the significant morbidity of extirpative surgery (radical cystectomy and urinary diversion), there have also been greater efforts to evaluate bladder-sparing protocols and improve the selection of patients for surgery and their postoperative recovery. The authors review special considerations for organ-sparing surgery in females, geriatric co-management, and enhanced recovery after surgery protocols. For upper tract urothelial carcinoma, there has been increasing recognition of its unique diagnostic and therapeutic challenges, including risks of renal functional loss. There have been advances in molecular profiling that have demonstrated various genomic differences between upper tract urothelial carcinoma and UCB, with treatment implications. This article reviews studies evaluating perioperative care that focused on optimizing therapeutic approaches, including neoadjuvant/adjuvant chemotherapy and immunotherapy, as well as nephron-sparing strategies in carefully selected cases.

KEYWORDS
nonmuscle invasive bladder neoplasms, perioperative care, urinary bladder neoplasms, urologic neoplasms

INTRODUCTION

The urothelium refers to the mucosal lining covering the surface of the renal calyces and pelvis, ureters, bladder, and urethra. This mucosal lining is prone to malignant transformation, denoting the term *urothelial carcinoma*, which represents the ninth most common malignancy worldwide.[1] Smoking is the most important risk factor, followed by occupational exposure (aromatic amines, agent orange, phenacetine), and chronic inflammatory conditions (schistosomiasis, chronic cystitis).[2] Depending on the anatomic location at presentation, urothelial carcinoma is commonly categorized as *urothelial carcinoma of the bladder* (UCB), which represents approximately 90%–95% of cases, and *upper tract urothelial carcinoma* (UTUC), representing 5%–10% of cases, whereas rare cases of urothelial carcinoma can arise in the urethra.[3,4] Upper tract involvement includes any region from the renal calyces to the distal ureter and is often associated with a more aggressive prognosis.[5] Urothelial carcinoma is a highly challenging malignancy that is associated with substantial mortality, morbidity, and economic cost.[3,4,6–9]

Historically, the management of UTUC has been extrapolated from treatment pathways derived from UCB. However, there has been increasing recognition of UTUC as a distinct entity with unique diagnostic and therapeutic challenges, including risks of renal functional loss. Therefore, dedicated pathways of management have been developed through UTUC guidelines from both American and European urological associations.[10,11] Recent advances in molecular profiling have demonstrated that fibroblast growth factor receptor 3 (*FGFR3*) and *HRAS* alterations are more prevalent in UTUC, whereas *TP53*, *ERBB2*, and *RB1* mutations are more predominant in UCB, which may have treatment implications as well.[12–19]

Overall, there have been significant advances in the treatment paradigms for both UCB and UTUC, as discussed in this comprehensive review. We focus on novel therapeutic and diagnostic approaches to both disease entities in the perioperative setting, with an emphasis on patient-centered and individualized care. For muscle-invasive bladder cancer (MIBC), we highlight the perioperative use of immunotherapy and antibody–drug conjugates (ADCs), followed by bladder-sparing protocols and novel biomarkers. For nonmuscle-invasive bladder cancer (NMIBC), we discuss developments in the treatment of bacillus Calmette–Guerin (BCG)-unresponsive disease, unmet needs in clinical trial design, and the impact of variant histology. In terms of radical surgery, we discuss the role of extended lymph node dissection, special considerations for female and geriatric populations, as well as enhanced recovery protocols. For UTUC, we review the emergence of perioperative systemic therapy, organ-sparing management, the significance of genomic alterations, and improvements in risk assessment.

ADVANCES IN BLADDER CANCER

UCB represents a disease spectrum that ranges from nonmuscle-invasive tumors, which can be treated with endoscopic resection and/or intravesical therapy, to muscle-invasive tumors, which typically are managed with systemic therapy and radical surgery or radiotherapy. NMIBC represents approximately 75% of organ-confined disease, whereas the remaining 25% is MIBC.[20]

Muscle-invasive bladder cancer

Because of the propensity for metastasis, a standard of care for patients with MIBC is neoadjuvant cisplatin-based chemotherapy followed by radical cystectomy and urinary diversion, particularly for patients who have adequate kidney function. Despite this aggressive approach, survival outcomes remain unfavorable, and one half of patients will experience recurrence or progression and death within 5 years.[21] This potentially poor prognosis contributes to the high rates of depression and anxiety (up to 78% and 71%, respectively) seen even after treatment in patients with bladder cancer.[22] Moreover, approximately one half of patients are not cisplatin-eligible because of comorbidities. Fortunately, advances in nonplatinum-based therapies, specifically immunotherapy and ADCs, have expanded the therapeutic arsenal for patients with MIBC in both the neoadjuvant and adjuvant settings and have been shown to improve survival outcomes (Table 1). Given the significant morbidity of extirpative surgery (radical cystectomy and urinary diversion), there have also been greater efforts to evaluate bladder-sparing protocols and improve our selection of patients for a surgical approach and their postoperative recovery.

Immunotherapy in the perioperative setting

There have been multiple phase III trials assessing the role of immunotherapy in the perioperative setting for patients with MIBC. The first reported was the IMvigor010 trial (ClinicalTrials.gov identifier NCT02450331), which randomly assigned patients with MIBC who had undergone radical cystectomy to either adjuvant atezolizumab (antiprogrammed death 1 ligand [anti–PD-L10 antibody) or observation.[23] Unfortunately, the trial did not meet its primary end point of improved disease-free survival (DFS) in the atezolizumab group compared with observation (median DFS, 19.4 vs. 16.6 months; $p = .24$).[23] In contrast, the CheckMate 274 trial (ClinicalTrials.gov identifier NCT02632409), which enrolled patients with high-risk MIBC after radical cystectomy ($n = 709$) and randomly assigned them to either adjuvant nivolumab (antiprogrammed death 1 [anti–PD-1] antibody) or placebo, demonstrated prolonged median DFS with adjuvant nivolumab (20.8 vs. 10.8 months; $p < .001$) using an intention-to-treat analysis.[24] A subsequent report indicated a median overall survival (OS) benefit with nivolumab (hazard ratio [HR] 0.76; 95% confidence interval [CI], 0.61–0.96).[25] In addition, the AMBASSADOR trial (ClinicalTrials.gov identifier NCT03244384) enrolled more than 700 patients who had high-risk MIBC after radical cystectomy to either adjuvant pembrolizumab (anti–PD-1 antibody) or observation.[26] Pembrolizumab resulted in a significant improvement in median DFS compared with observation (29.6 vs. 14.2 months; $p = .003$).[26] Final OS data remain immature, but, at the

TABLE 1 Perioperative studies on treatments for localized muscle-invasive bladder cancer (completed and ongoing trials).

Clinical trial/NCT identifier	Condition	Location/design	Experimental intervention	Primary outcomes for evaluation	Trial status
Neoadjuvant treatments					
Alliance A031701, phase 2/ NCT03609216	MIBC	Multicenter, USA/ nonrandomized, open-label	Neoadjuvant gemcitabine and cisplatin, followed by bladder-sparing surgery; gemcitabine and cisplatin, followed by chemoradiotherapy + radical cystectomy	3-year RFS rate	Ongoing (recruiting)
S1806, phase 3/ NCT03775265	MIBC	Multicenter, USA/ randomized, open-label	Neoadjuvant chemoradiotherapy + atezolizumab, followed by TURBT	BI-EFS	Ongoing (active; not recruiting)
RETAIN BLADDER, phase 2/ NCT02710734	MIBC	Multicenter, USA/ nonrandomized, open-label	Neoadjuvant bladder-sparing treatment combinations of TURBT; accelerated methotrexate, vinblastine, doxorubicin, and cisplatin; and/or chemoradiotherapy, followed by further TURBT or radical cystectomy	Metastasis-free survival at 2 years	Ongoing (active; not recruiting)
ChiCTR2100050763	MIBC (T2–T4aN0–N1M0)	Single-center, China	Neoadjuvant cisplatin/ carboplatin + gemcitabine + tislelizumab, followed by partial/radical cystectomy or TURBT	Bladder-preservation rate	Ongoing
PURE-01, phase 2/ NCT02736266	MIBC (T2–T4aN0) with residual disease after TURBT	Single-center, Italy/open-label	Neoadjuvant pembrolizumab, followed by radical cystectomy	Pathologic complete response	Completed (2022)
LC 2015L12, phase 2/NCT02861196	MIBC (T2–T4aN0M0)	Single-center, China/open-label	Neoadjuvant gemcitabine/cisplatin, followed by trimodal therapy (TURBT, TURBT + BCG, TURBT + concurrent cisplatin-based chemoradiotherapy, traditional Chinese medicine, or second-line chemotherapy)	Bladder preservation rate	Completed (2018)
HCRN GU16-257, phase 2/ NCT03558087	MIBC	Multicenter, USA/open-label	Neoadjuvant gemcitabine + cisplatin + nivolumab, followed by cystectomy or maintenance therapy with nivolumab	2-year clinical CRR, benefit from treatment	Completed (2024)
TRUCE-01, phase 2/ NCT04730219	MIBC	Single-center, China/open-label	Neoadjuvant tislelizumab + nab-paclitaxel, followed by complete TURBT or radical cystectomy	Clinical CRR	Unknown status (was estimated to be completed by July 2024)
SURE-01, phase 2/ NCT05226117	MIBC (in patients who cannot, or are unwilling to, receive cisplatin-based chemotherapy)	Single-center, Italy/ nonrandomized, open-label, single cohort	Neoadjuvant SG monotherapy, followed by radical cystectomy	Pathologic complete response	Unknown (was estimated to be completed by June 2023)
Adjuvant treatments					
IMvigor010, phase 3/NCT02450331	MIBC	Multicenter, global/ randomized, open-label	Adjuvant atezolizumab (after surgical resection, including radical cystectomy and lymph node dissection)	DFS (up to ~50 months)	Terminated early; did not meet primary end point
CheckMate 274, phase 3/ NCT02632409	High-risk MIBC	Multicenter, global/ randomized, double-blind	Adjuvant nivolumab (after radical surgical resection, including radical cystectomy)	DFS; DFS in population with PD-L1 expression ≥1% (both up to ~4 years)	Ongoing (active; not recruiting)
AMBASSADOR, phase 3/ NCT03244384	High-risk MIBC	Multicenter, USA/ randomized, open-label	Adjuvant pembrolizumab (after surgical resection, including radical cystectomy and lymph node dissection)	OS; DFS (both up to 5 years)	Ongoing (active; not recruiting)

TABLE 1 (Continued)

Clinical trial/NCT identifier	Condition	Location/design	Experimental intervention	Primary outcomes for evaluation	Trial status
Neoadjuvant and adjuvant treatments					
SURE-02, phase 2/ NCT05535218	MIBC (in patients who cannot, or are unwilling to, receive cisplatin-based chemotherapy)	Single-center, Italy/ nonrandomized, open-label, single-cohort	Neoadjuvant SG + pembrolizumab, followed by cystectomy, followed by adjuvant pembrolizumab	Pathologic complete response	Ongoing (enrolling by invitation)
NURE-Combo, phase 2/ NCT04876313	MIBC	Single-center, Italy/ nonrandomized, open-label, single-center	Neoadjuvant nivolumab and nab-paclitaxel, followed by radical cystectomy, followed by adjuvant nivolumab	Pathologic complete response	Ongoing (recruiting)
EV-103, phase 1 & 2/NCT03288545	MIBC (cohorts H, J, and L)	Multicenter, global/ randomized, open-label, multicohort	Neoadjuvant EV, monotherapy, followed by radical cystectomy; neoadjuvant EV + pembrolizumab, followed by radical cystectomy; neoadjuvant EV, followed by radical cystectomy, followed by adjuvant EV	Pathologic CRR	Ongoing (active; not recruiting)
EV-303, phase 3/ NCT03924895	MIBC (patients who are cisplatin-ineligible or decline cisplatin)	Multicenter, global/ randomized, open-label	Perioperative (adjuvant + neoadjuvant) pembrolizumab, along with radical cystectomy + PLND; perioperative EV + pembrolizumab, along with radical cystectomy + PLND durvalumab	EFS	Ongoing (active; not recruiting)
EV-304, phase 3/ NCT04700124	MIBC (patients who are cisplatin-eligible)	Multicenter, global/ randomized, open-label	Perioperative (adjuvant + neoadjuvant) EV + pembrolizumab, along with radical cystectomy + PLND durvalumab	EFS	Ongoing (active; not recruiting)
NIAGARA phase 3/ NCT03732677	MIBC	Multicenter, global/ randomized, open-label	Neoadjuvant durvalumab + gemcitabine/ cisplatin, followed by cystectomy, followed by adjuvant durvalumab	Pathologic CRR (at cystectomy; up to 6 months); EFS (up to 4 years)	Ongoing (active; not recruiting)
VOLGA, phase 3/ NCT04960709	MIBC (patients undergoing radical cystectomy who are cisplatin-ineligible or decline cisplatin)	Multicenter, global/ randomized, open-label	Neoadjuvant durvalumab + tremelimumab + EV, followed by radical cystectomy, followed by adjuvant tremelimumab and durvalumab cycles; neoadjuvant durvalumab + EV, followed by radical cystectomy, followed by adjuvant durvalumab	EFS; frequency of adverse events; vital signs	Ongoing (active; not recruiting)

Abbreviations: BCG, bacillus Calmette–Guérin; BI-EFS, bladder-intact event-free survival; CRR, complete response rate; DFS, disease-free survival; EFS, event-free survival; EV, enfortumab vedotin; MIBC, muscle-invasive blader cancer; NA, not applicable/available; NMIBC, nonmuscle-invasive bladder cancer; nab-paclitaxel, nanoparticle albumin-bound paclitaxel; NCT, ClinicalTrials.gov identifier; OS, overall survival; PFS, progression-free survival; PLND, pelvic lymph node dissection; RFS, recurrence-free survival; SG, sacituzumab govitecan; TURBT, transurethral resection of bladder tumor.

second interim analysis, there was no significant difference in 3-year OS between the groups (HR, 0.98; 95% CI, 0.76–1.26).[26]

Finally, the phase 3 NIAGARA trial (ClinicalTrials.gov identifier NCT03732677) enrolled more than 1060 patients with MIBC, all of whom were treated with cisplatin and gemcitabine in the neoadjuvant setting before undergoing radical cystectomy. Patients were randomly assigned to either neoadjuvant durvalumab (anti–PD-L1 antibody) followed by maintenance durvalumab (n = 533) or no additional treatment (n = 530).[27] The addition of perioperative durvalumab to neoadjuvant chemotherapy (NAC) yielded significant improvements in 2-year event-free survival (EFS; durvalumab, 67.8% vs. 59.8% with chemotherapy alone; $p < .001$) and 2-year OS (durvalumab, 82.2% vs. 75.2% with chemotherapy alone; $p = .01$).[27]

Overall, these clinical trials have expanded the therapeutic options available to patients with muscle-invasive disease and favor the inclusion of immune checkpoint inhibitor (ICI)-based combination

regimens with platinum-based therapies. The results of the CheckMate 274 trial led to the US Food and Drug Administration (FDA) approval of adjuvant nivolumab, which is now a standard of care in this setting. The results of the NIAGARA trial led to the FDA approval of perioperative durvalumab (neoadjuvant and adjuvant, or *sandwich immunotherapy*), which also is now a standard of care. Studies of neoadjuvant immunotherapy alone are limited to smaller phase 1 and 2 trials, thus larger trials with demonstrable survival benefits are still needed before this becomes standard practice. Of note, ICIs can affect virtually any organ system and are most commonly associated with dermatologic, gastrointestinal, endocrine, pulmonary, and hepatic toxicities, often requiring timely recognition and management to avoid severe complications.[28]

Treatment using antibody–drug conjugates

ADCs are designed to carry cytotoxic chemotherapy agents to specific antigenic targets expressed on the cell surface, leading to internalization and, eventually, cell death.[29,30] Nectin-4 is a tumor-associated antigen expressed in most urothelial cancers.[29] Enfortumab vedotin (EV), an anti–nectin-4 ADC, was evaluated in patients with locally advanced or metastatic disease in the phase 3 EV-301 and EV-302 trials (ClinicalTrials.gov identifiers NCT34744107 and NCT04223856, respectively), which compared EV as monotherapy or in combination with pembrolizumab, respectively, versus chemotherapy alone. In EV-301, EV demonstrated improvements in both median progression-free survival (PFS; 5.55 vs. 3.71 months; $p < .001$) and median OS (12.88 vs. 8.97 months; $p = .001$) compared with investigator-chosen chemotherapy (either docetaxel, paclitaxel, or vinflunine).[31] In EV-302, EV plus pembrolizumab demonstrated further improvements in both median PFS (12.5 vs. 6.3 months; $p < .001$) and median OS (31.5 vs. 16.1 months; $p < .001$) compared with gemcitabine plus cisplatin or carboplatin.[32] Given its efficacy, EV was then evaluated in the setting of localized MIBC in patients who could not receive cisplatin-based chemotherapy in the phase 2 EV-103 trial (ClinicalTrials.gov identifier NCT03288545).[33] Patients received neoadjuvant EV before undergoing cystectomy, and demonstrated a pathologic complete response rate (CRR) of 36% and a pathologic downstaging rate of 50%.[34] One-year EFS was 76.4%, and 2-year EFS was 62%.[33,34] All patients were able to undergo surgery with no recorded delays because of EV-related adverse events, which most commonly entail fatigue, diarrhea, maculopapular rash, and/or peripheral sensory neuropathy, that can affect treatment tolerability and require proactive management.[35]

The TROPHY-U-01 phase 2 trial (ClinicalTrials.gov identifier NCT03547973) assessed the efficacy of sacituzumab govitecan (SG), an antitrophoblast cell-surface antigen 2 (anti-Trop-2) ADC, in patients with metastatic urothelial carcinoma and demonstrated an objective response rate (ORR) of 28%.[36] This led to an accelerated approval from the FDA. However, the objective of the TROPiCS-04 phase 3 trial (ClinicalTrials.gov identifier NCT04527991) was to confirm the phase 2 results but failed to meet its primary end point of OS (median OS, 10.3 vs. 9.0 months with SG vs. chemotherapy, respectively; $p = .087$).[37] Consequently, FDA approval of SG as treatment for urothelial carcinoma in the United States was withdrawn by the sponsor.[38] The future of SG in urothelial cancer remains unclear, although the results of the Double Antibody–Drug Conjugate phase 1 trial (ClinicalTrials.gov identifier NCT04724018), which evaluated EV in combination with SG in patients with metastatic urothelial carcinoma who experienced disease progression after platinum chemotherapy and/or immunotherapy, produced an ORR of 70%, with three patients achieving a complete response, suggesting that combinations of ADCs might prove useful in other settings.[39] Physicians should closely monitor patients receiving SG because of its notable hematologic toxicity profile, particularly anemia and neutropenia, which may necessitate dose adjustments or limit continued therapy.[35]

Trastuzumab deruxtecan (T-DXd) is an ADC that targets HER-2 expression on the surface of cancer cells. The DS8201-A-U105 phase 1b trial (ClinicalTrials.gov identifier NCT03523572) evaluated T-DXd in combination with nivolumab for patients with HER2-expressing advanced or metastatic urothelial carcinoma who had progression on platinum-based chemotherapy. In patients with HER2-positive disease (defined as an immunohistochemical [IHC] HER2 expression level of 2+ or 3+), the combination resulted in an ORR of 36%, a median PFS of 6.9 months, and a median OS of 11.0 months.[40] This was followed by the DESTINY-PanTumor02 phase 2 trial (ClinicalTrials.gov identifier NCT04482309), which evaluated the efficacy of T-DXd in previously treated, locally advanced or metastatic, HER2-positive (IHC 2+/3+) solid tumors, including endometrial, cervical, ovarian, bladder, biliary tract, and pancreatic cancer.[41] Across all cohorts, the ORR was 37.1% (95% CI, 31.3%–43.2%), with higher response rates in patients with IHC 3+ tumors. The ORR for patients with IHC 3+ bladder tumors was 56.3% (95% CI, 29.9%–80.2%), whereas the median PFS was 7.4 months (95% CI, 3.0–11.9 months), and the median OS was 13.4 months (95% CI, 6.7–19.8 months). These results led to the accelerated FDA approval of this drug for adult patients with unresectable or metastatic, HER2-positive, IHC 3+ solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options.[41,42] T-DXd is associated with specific adverse events, including nausea, vomiting, fatigue, myelosuppression (neutropenia, anemia, thrombocytopenia), alopecia, diarrhea, and elevations in liver enzymes. Clinicians should be vigilant for more serious toxicities, notably, interstitial lung disease/pneumonitis and cardiotoxicity.

Given the promising results of ADCs in advanced UCB, further efforts are being made to evaluate the role of ADCs in the neoadjuvant and adjuvant settings, with or without combination immunotherapy. These phase 3 trials in patients with MIBC undergoing radical cystectomy include: KEYNOTE-905/EV-303 (perioperative pembrolizumab vs. pembrolizumab with EV in patients who are cisplatin-ineligible),[43] KEYNOTE-B15/EV-304 (perioperative pembrolizumab with EV vs. chemotherapy in patients who are cisplatin-eligible),[44] and VOLGA (neoadjuvant durvalumab plus tremelimumab [anti-CTLA-4 antibody] plus EV vs. durvalumab plus EV in patients who are cisplatin-

ineligible; ClinicalTrials.gov identifier NCT04960709).[45] In the 2025 National Comprehensive Cancer Network (NCCN) guidelines, EV with pembrolizumab is now the preferred first-line systemic therapy regimen for locally advanced disease (as downstaging therapy) or metastatic disease. EV is also the preferred second-line option for patients who have received a checkpoint inhibitor and are chemotherapy-naive but cannot receive cisplatin.

Bladder-sparing protocols for MIBC

The 2025 NCCN guidelines list two category 1 options for stage II and IIIA MIBC: radical cystectomy with NAC or bladder preservation with chemoradiotherapy. Complications are reportedly as high as 60% after radical cystectomy within the 90-day postoperative period.[46] Because most patients with MIBC are older than 65 years and/or have significant comorbidities, and because organ preservation is of utmost importance to patient quality of life, identifying bladder-sparing regimens that can achieve comparable outcomes regarding disease control is critical.

Trimodal therapy refers to maximal transurethral resection of bladder tumor (TURBT) followed by concurrent chemoradiation.[47] However, high-level data supporting the effectiveness of this approach compared to cystectomy is lacking. The SPARE trial (International Standard Randomized Controlled Trial Number [ISRTCN] identifier ISRTCN61126465) attempted to randomize patients to NAC and radical cystectomy versus bladder preservation, but it closed early because of poor accrual.[48] Zlotta et al. performed a retrospective analysis of 722 patients from three institutions with clinical T2–T4N0M0 (c T2–T4N0M0) MIBC, of whom 440 underwent radical cystectomy and 282 received trimodal therapy. By using statistical methods to match patients between the two groups for comparison (propensity score matching [PSM] and inverse probability treatment weighting), the results yielded comparable outcomes. Five-year cancer-specific survival (CSS) for radical cystectomy versus trimodal therapy was 83% versus 85%, respectively, with PSM. Similarly, the 5-year DFS rate was 76% versus 76%, respectively, with PSM.[49] Five-year OS favored trimodal therapy (PSM: 72% vs. 77%; $p = .0078$). Of 282 patients treated with trimodal therapy, cystectomy was performed in a relatively low number of patients ($n = 38$; 13%), the vast majority because of an invasive recurrence. These results support the notion that both treatment approaches provide comparable oncologic outcomes in selected patients with MIBC.

Multiple prospective Radiation Therapy Oncology Group (RTOG) protocols have sought to evaluate bladder-preserving combined-modality therapy options in patients with MIBC, including five phase 2 trials (RTOG 8802, 9506, 9706, 9906, and 0233) and one phase 3 trial (RTOG 8903). Mak et al. performed a pooled analysis of the long-term outcomes of patients enrolled across these trials, spanning 468 patients with MIBC. A complete response to trimodal therapy was documented in 69% of patients, and the 5-year and 10-year OS rates for this population were 57% and 36%, respectively.[50] One hundred patients (21%) who were enrolled in the six trials ultimately underwent cystectomy; 62% for an incomplete response to induction chemotherapy and radiotherapy, and 36% underwent cystectomy because of recurrence. A multidisciplinary discussion and shared decision making remain keys to success with these approaches.

In addition, prospective trials have evaluated bladder preservation in patients who were not cisplatin-eligible. The BC2001 (ISRTCN68324339) trial included patients with cT2–T4aN0 MIBC and randomly assigned them to either radiotherapy or chemoradiotherapy using fluorouracil and mitomycin C. Chemoradiotherapy resulted in better locoregional control over radiotherapy alone based on 2-year recurrence-free survival (RFS; HR, 0.68; $p = .03$).[51,52] This trial demonstrated that the addition of chemotherapy to radiotherapy does not affect patient-reported quality of life.[53] RTOG 0712 also included patients with cT2–T4a MIBC and randomly assigned them to either fluorouracil with cisplatin and twice daily radiation or low-dose gemcitabine and once daily radiation as part of bladder preservation. This low-dose gemcitabine regimen led to a 3-year bladder-intact distant metastasis-free survival rate similar to that of the cisplatin-based regimen (distant metastasis-free survival: 84% vs. 78% for low-dose gemcitabine vs. gemcitabine and fluorouracil plus cisplatin, respectively, with bladder-intact distant metastasis-free survival rates of 72% and 67%, respectively).[54]

Patient-reported quality of life has been reported to deteriorate during trimodal therapy because of treatment-related side effects but improves to at least pretreatment levels within 6 months.[53] In a long-term comparative study, both trimodal therapy and radical cystectomy resulted in good long-term health-related quality of life outcomes in MIBC survivors. Multivariable analysis revealed that trimodal therapy improved the general quality of life by 9.7 points (on a scale from 0 to 100) compared with radical cystectomy ($p = .001$) and enhanced the scores for physical, cognitive, emotional, and social functioning by 6.6–9.9 points ($p \leq .04$). Although trimodal therapy did not significantly affect urinary symptom scores compared with radical cystectomy, it was associated with improved sexual function (by 8.7–32.1 points; $p \leq .02$) and body image (by 14.8 points; $p < 0.001$).[55]

The TRUCE-01 phase 2 trial (ClinicalTrials.gov identifier NCT04730219) included patients with MIBC and evaluated a bladder-sparing approach using tislelizumab (anti–PD-1) plus nanoparticle albumin-bound paclitaxel followed by maximal TURBT and/or radical cystectomy.[56] The bladder-sparing approach of maximal TURBT ($n = 24$) produced a clinical complete response in 17 patients and a partial response in six patients (NMIBC disease only). Of the 24 patients who underwent radical cystectomy, eight patients had a pathologic complete response, and one patient had a partial response.[56] Similarly, Zeng et al. reported the preliminary results of a trial evaluating cisplatin or carboplatin in combination with gemcitabine and tislelizumab as neoadjuvant therapy in patients with MIBC. Of 17 patients enrolled at the time of this publication, 10 had a clinical complete response and avoided cystectomy, one had no response, and two had a clinical partial response and underwent

cystectomy after disease progression.[57] Although both of these trials suggest that neoadjuvant immunotherapy regimens may play a role in patients hoping to undergo bladder-sparing treatments, other trials have not been favorable enough to fully adopt this approach. This includes the PURE-01 trial (ClinicalTrials.gov identifier NCT02736266), which revealed a 42% pathologic CRR with pembrolizumab,[58] and the phase 2 trial of gemcitabine, cisplatin, and nivolumab, which demonstrated a clinical CRR of 43%.[59] The addition of immunotherapy to trimodal therapy is an area of active investigation, and we await results of ongoing trials to better inform its role.[60,61]

Future research in this area should involve clinical investigations of risk-adapted approaches to identify patients for bladder preservation. Some completed and ongoing risk-adapted clinical trials to determine whether biomarker selection can prospectively identify patients for bladder preservation have demonstrated promise. The RETAIN 1 phase 2 trial (ClinicalTrials.gov identifier NCT02710734) included patients with MIBC after undergoing NAC (accelerated methotrexate, vinblastine, doxorubicin, and cisplatin) in an effort to prospectively identify patients for a cystectomy or chemoradiation-avoidance algorithm.[62] The authors sequenced pre-NAC TURBT specimens for mutations in *ATM*, *ERCC2*, *FANCC*, or *RB1*. Patients who had one or more mutation(s) and no clinical evidence of disease identified on restaging TURBT, urine cytology, and imaging after NAC were allocated to active surveillance. The remaining patients underwent bladder-directed therapy. The 2-year metastasis-free survival rate was 76.0% in the surveillance group and 71.1% in all other patients, whereas the 2-year OS rates were 88.0% and 82.2%, respectively. Although the primary end point of the study (2-year metastasis-free survival) was not reached, 17% of all enrolled patients and 48% of surveilled patients were able to avoid cystectomy without metastatic disease.[62] The ongoing Alliance A031701 trial (ClinicalTrials.gov identifier NCT03609216) also seeks to determine whether patients with MIBC and specific DNA damage-repair gene alterations (*BRCA1*, *BRCA2*, *ATM*, *ATR*, *FANCC*, *RECQL4*, *RAD51C*, *ERCC2*, and *ERCC5*) who exhibit a <T1 response on clinical restaging after NAC (gemcitabine plus cisplatin) can safely proceed with organ preservation. The primary end point is 3-year EFS in patients with DNA damage-repair gene alterations who undergo organ-sparing management.[63]

Novel diagnostic biomarkers

Circulating tumor DNA

Circulating tumor DNA (ctDNA) is tumor-shed cell DNA circulating in plasma with diagnostic and prognostic implications. ctDNA assays can be tumor-informed, relying on prior genomic profiling of tumor tissue, or tumor-agnostic, which are independent of any prior genomic knowledge. Preliminary studies evaluating the utility of ctDNA as a tool to predict a complete response to therapy and avoid cystectomy in selected patients are underway. For example, Dyrskjøt et al. analyzed baseline and precystectomy ctDNA levels with a tumor-informed assay (Signatera; Natera Inc.) in 68 patients with MIBC. Their results indicated that the probability of patients who had negative ctDNA results achieving a pathologic complete response was significantly greater than that of those who had positive ctDNA results ($p < .0001$) and that ctDNA status at baseline and before cystectomy was a better predictor for RFS than a pathologic complete response (HR, 8.5 [$p < .0001$] and 14.0 [$p < .0001$], respectively).[64] External validation of this method is still warranted, but it establishes the potential of analyzing ctDNA levels to make more informed decisions about whether to proceed with cystectomy based on the individual patient's risk of recurrence.

In the context of surgical tumor resection, ctDNA may yield enough sensitivity to monitor disease recurrence after radical cystectomy and help select patients who may benefit from adjuvant therapy. A subgroup analysis of the IMvigor010 trial demonstrated that patients who were positive for ctDNA with a tumor-informed assay (Signatera) had improved DFS with adjuvant atezolizumab compared with patients undergoing observation (HR, 0.58; $p = .0024$).[23] A follow-up study reported that patients who were positive for ctDNA had improved OS with adjuvant atezolizumab compared with those who underwent observation (HR, 0.59; 95% CI, 0.42–0.83), and the degree of ctDNA reduction (100% clearance vs. 50%–99% reduction vs. <50% reduction) was also associated with OS.[65] Crupi et al. performed a systematic review of prospective studies exploring NAC/adjuvant chemotherapy/immunotherapy in 845 patients with MIBC (T2–T4a, any N, and M0) treated with radical cystectomy. They observed that changes in ctDNA levels, evaluated with various tumor-informed assays, predicted radiologic progression, and recurrence was diagnosed within a median 101 days after ctDNA detection.[66]

In a retrospective analysis of the KEYNOTE-361 trial (ClinicalTrials.gov identifier NCT02853305), Powles et al. evaluated the association of pretreatment and posttreatment ctDNA, using both tumor-informed and tumor-agnostic assays, with clinical outcomes in a subset of patients who received pembrolizumab ($n = 130$) or chemotherapy ($n = 130$). Lower baseline ctDNA was associated with improved overall response ($p = .009$), PFS ($p < .001$), and OS ($p < .001$) for patients who received pembrolizumab but not for those who received chemotherapy ($p > .05$ for all). The results were similar with both tumor-informed and tumor-agnostic assays.[67]

Other potential biomarkers

Irisin, a myokine secreted from myocytes in response to muscle contraction, has been implicated in the progression of multiple cancer types by contributing to an inflammatory microenvironment and carcinogen synthesis.[68] Taken et al. evaluated serum irisin levels in 90 patients, including 60 with NMIBC and 30 with MIBC, and compared them with 30 age-matched, healthy controls. Mean serum irisin levels were significantly lower both in the bladder cancer group relative to the control group and in the MIBC group relative to the NMIBC group. Overall, serum irisin levels yielded a sensitivity of 86.2% and a specificity of 89.7% at a cutoff value of 8.69 (area under the curve, 0.86) to identify patients with bladder cancer.[68]

The cysteine-rich angiogenic inducer 61 (CYR61) protein plays a role in multiple physiologic functions, including tissue repair, cellular adhesion, migration, and proliferation.[69] Chen et al. evaluated the differential gene expression of CYR61 between 14 MIBC and 16 NMIBC tumor samples. Their results demonstrated that CYR61 transcript levels were 3.34-fold higher ($p < .001$) in the MIBC samples than in the NMIBC samples.[69] This preliminary evidence suggests that CYR61 can serve as a promising biomarker to identify muscle-invasive disease.

Novel prognostic biomarkers

TIGIT/PD-1

Within the tumor microenvironment, PD-1 and TIGIT are immune checkpoints expressed after T-cell receptor stimulation and are in charge of mediating T-cell suppression and dysfunction.[70] Liu et al. evaluated the significance of TIGIT and PD-1 expression in patients with MIBC. Those authors categorized patient tumors into cluster I (TIGIT-low and PD-1–low), which contained low levels of immune infiltrates with higher *FGFR3* mutation; cluster II (TIGIT-low and PD-1–high), which exhibited a highly infiltrated microenvironment with increased cytolytic CD8-positive T cells; and cluster III (TIGIT-high), which presented a suppressive tumor microenvironment characterized by exhausted CD8-positive T cells. Patients with TIGIT-high expression had a better OS with adjuvant chemotherapy ($p = .001$), unlike the patients in cluster I ($p = .511$) and cluster II ($p = .637$). Although patients in cluster III exhibited worse outcomes, they also had an activated immunotherapeutic and EGFR-associated pathway with greater potential to benefit from adjuvant chemotherapy and anti–PD-L1 immunotherapy.[70]

DNA methylation

A study performed by Xu et al. evaluated molecular data from 413 patients with MIBC to characterize DNA methylation-based signatures as a prognostic model for OS. The authors compared DNA methylation-based risk scores as an independent indicator of mortality with individual clinicopathologic features (age, sex, smoking status, tumor [T] classification, and lymph node [N] category). The results revealed higher area under the curve scores for DNA methylation–based risk scores at the 3-year and 5-year time points. After performing univariate and multivariate analyses, the DNA methylation–based classifier remained an independent prognostic indicator. This preoperative risk classification can enhance personalized clinical decision making in this patient population.[71]

Urine PD-L1

PD-L1 has been established as a predictive biomarker for therapeutic response to immunotherapy in urothelial carcinoma.[72,73] However, tissue sampling and subsequent molecular analysis are prone to underscoring the degree of PD-L1 expression because of a heterogeneous tumoral tissue landscape. The identification of urine PD-L1 (uPD-L1) was evaluated by Ma et al. in 138 patients with MIBC as a prognostic biomarker to predict recurrence risk. Univariate analysis demonstrated that a one-unit increase in uPD-L1 increased the likelihood of recurrence in MIBC by 110% ($p = .048$). Survival analysis revealed that patients who had MIBC with high uPD-L1 levels had a shorter RFS than patients with low uPD-L1 levels, although this finding did not indicate statistical significance ($p = .24$).[74]

Nonmuscle-invasive bladder cancer

NMIBC presents a host of perioperative concerns for which investigations are ongoing, including unresponsiveness to intravesical therapies, the risk of poor oncologic outcomes because of variant histology, and the need for improved metrics for toxicity in clinical trials.

Treatment options for BCG-unresponsive NMIBC

The International Bladder Cancer Group defines BCG-unresponsiveness as a condition that satisfies one or more of the following criteria: (1) persistent/recurrent carcinoma in situ within 1 year of completing adequate BCG treatment (occurring with or without nonmuscle-invasive papillary disease); (2) recurrent high-grade tumor (Ta/T1) within 6 months of completing adequate BCG treatment; and/or (3) high-grade tumor (T1) upon first assessment after BCG induction.[75,76] Adequate BCG is defined as the receipt of at least five of six doses of the induction course plus at least two of three doses of the first maintenance cycle or five of six doses of an additional induction course. Nearly 33% of patients with NMIBC do not respond to BCG therapy, prompting the search for alternative treatment options for patients who have BCG-unresponsive disease (Table 2).[77] Several novel therapies have been approved in the BCG-refractory space, including adenoviral vector-based intravesical gene therapy (nadofaragene firadenovec), intravesical immunotherapy (nogapendekin alfa inbakicept or N-803), and pembrolizumab. The combination of gemcitabine, which inhibits DNA replication, and docetaxel, which causes cell cycle arrest and induces apoptosis, has been extensively used and reported on in a retrospective fashion for BCG-unresponsive disease, whereas the ongoing BRIDGE trial (ClinicalTrials.gov identifier NCT05538663) will evaluate its efficacy in BCG-naive disease.[75,78] This trial is expected to reach completion by 2029.[79]

Newly approved N-803 is an interleukin-15 superagonist that stimulates natural killer cells and effector and memory T cells.[80,81] The multicenter QUILT-3.032 phase 2/3 trial (ClinicalTrials.gov identifier NCT03022825) enrolled patients with BCG-unresponsive NMIBC and assessed the efficacy of N-803, either alone or in combination with BCG.[80,81] Treatment with intravesical N-803 plus BCG in patients who had carcinoma in situ with or without Ta/T1 papillary tumors ($n = 82$) resulted in a CRR of 71%; those who had a complete response had 2-year cystectomy-free survival and CSS rates of 89.2% and 100%, respectively. In addition, treatment with N-803 plus BCG in patients with high-grade, Ta/T1 papillary disease ($n = 72$) achieved a 1-year DFS rate of 55.4%.[81]

TABLE 2 Perioperative studies on treatments for nonmuscle-invasive bladder cancer (completed and ongoing trials).

Clinical trial/ NCT identifier	Condition	Location/design	Experimental intervention	Primary outcomes for evaluation	Trial status
rAd-IFN-CS-003, phase 3/ NCT02773849	High-grade, BCG-unresponsive NMIBC	Multicenter, USA/ open-label	Intravesical nadofaragene firadenovec	1-year CRR	Completed (2023)
BOND-003, phase 3/ NCT04452591	BCG-unresponsive NMIBC	Multicenter, global/ nonrandomized, open-label, multicohort	Intravesical cretostimogene grenadenorepvec	3-year CRR; 3-year high-grade EFS	Ongoing (recruiting)
KEYNOTE-057, phase 2/ NCT02625961	BCG-unresponsive, high-risk NMIBC	Multicenter, global/ randomized, open-label, multicohort	Pembrolizumab	CRR; 1-year DFS; frequency of adverse events; study discontinuance because of adverse events	Ongoing (active; not recruiting)
Alliance A031803, phase 2/ NCT04164082	BCG-unresponsive NMIBC	Multicenter, USA/ open-label	Intravesical gemcitabine + pembrolizumab	6-month CRR; 18-month EFS	Ongoing (recruiting)
SWOG S1605, phase 2/ NCT02844816	Recurrent, BCG-unresponsive NMIBC	Multicenter, USA and Canada/open-label	Atezolizumab	25-week CRR; 18-month EFS	Ongoing (active; not recruiting)
KEYNOTE-676, phase 3/ NCT03711032	High-risk NMIBC (persistent/ recurrent after BCG induction or BCG-naive)	Multicenter, global/ randomized, open-label, multicohort	BCG + pembrolizumab	CRR; EFS	Ongoing (active; not recruiting)
CREST, phase 3/ NCT04165317	High-risk, BCG-naive NMIBC; BCG-unresponsive NMIBC	Multicenter, global/ randomized, open-label	BCG + sasanlimab (for BCG-naive NMIBC); sasanlimab monotherapy (for BCG-unresponsive NMIBC)	CRR; EFS	Ongoing (active; not recruiting)
POTOMAC, phase 3/ NCT03528694	High-risk, BCG-naive NMIBC	Multicenter, global/ randomized, open-label	BCG + durvalumab	DFS	Ongoing (active; not recruiting)
QUILT-3.032, phase 2 & 3/ NCT03022825	BCG-unresponsive, high-grade NMIBC	Multicenter, USA/ open-label	N-803, monotherapy or in combination with BCG	5-year complete response; 1-year DFS	Ongoing (active; not recruiting)
WO29635, phase 1b & 2/ NCT02792192	BCG-unresponsive, BCG-relapsing, or BCG-naive high-risk NMIBC	Multicenter, USA/ open-label	Atezolizumab, monotherapy or in combination with BCG	Frequency of adverse events; no. of participants with dose-limiting toxicities (BCG); maximum administered dose (BCG); 6-month CRR	Terminated early; primary end point met
ADAPT-BLADDER, phase 1 & 2/ NCT03317158	BCG-unresponsive, BCG-relapsing, or BCG-naive high-risk NMIBC	Multicenter, USA/ randomized, open-label	Durvalumab monotherapy; durvalumab + BCG; durvalumab + external-beam radiation therapy; durvalumab + gemcitabine/ intravesical docetaxel	Recommended phase 2 dose (for phase 1); 6-month CRR (for phase 2)	Ongoing (recruiting)
BRIDGE, phase 3/ NCT05538663	BCG-naive, high-grade NMIBC	Multicenter, USA/ randomized, open-label	Intravesical BCG; intravesical docetaxel and gemcitabine	2-year EFS	Ongoing (recruiting)
LEGEND, phase 1 & 2/ NCT04752722	BCG-unresponsive NMIBC; high-risk NMIBC (incompletely treated with BCG or BCG-naive)	Multicenter, USA and Canada/ nonrandomized, open-label	Intravesical EG-70	Cystoscopic CRR (at 48 weeks); frequency, nature, and severity of adverse events	Ongoing (recruiting)

Abbreviations: BCG, bacillus Calmette–Guérin; CRR, complete response rate; DFS, disease-free survival; EFS, event-free survival; NMIBC, nonmuscle-invasive bladder cancer; NCT, ClinicalTrials.gov identifier; SWOG, Southwest Oncology Group.

Although pembrolizumab, an antibody that inhibits PD-1, is approved for use in patients with BCG-unresponsive carcinoma in situ who are unwilling or ineligible to undergo radical cystectomy, the International Bladder Cancer Group recommends its use only after other bladder-sparing treatment options have been exhausted.[75,82] This is because of high toxicity, intermediate response, and durability of response. The multicenter KEYNOTE-057 phase 2 trial (ClinicalTrials.gov identifier NCT02625961) evaluated the safety and antitumor activity of pembrolizumab in patients with BCG-unresponsive, high-risk NMIBC.[82,83] At 3 months, a complete response was reported in 39 of 96 patients (41%) with BCG-unresponsive carcinoma in situ. Eighteen patients had a complete response at ≥12 months, and 20 experienced recurrent disease despite an initial complete response. There was no treatment-related mortality, but 8% of patients experienced serious treatment-related adverse events.[82] In a second cohort of 132 patients with BCG-unresponsive, high-risk, Ta or T1 bladder cancer, the results showed a 1-year DFS rate of 43.5%.[83] There was no treatment-related mortality, but 13% of the study population experienced serious treatment-related adverse events, such as colitis, autoimmune nephritis, and type 1 diabetes, among others.[83]

Similar to KEYNOTE-057, the Southwest Oncology Group SWOG S1605 trial (ClinicalTrials.gov identifier NCT02844816) evaluated atezolizumab (an antibody that inhibits PD-L1, reducing immunosuppressive signals in the tumor microenvironment) in patients who had BCG-unresponsive NMIBC (n = 172).[84,85] Twenty of the 74 patients (27%) with carcinoma in situ experienced a complete response at 6 months, and 56% of the responses were maintained for at least 12 months. For the 55 patients with Ta/T1 disease, the 18-month EFS rate was 49%. However, 12 of 129 patients experienced progression to muscle-invasive or metastatic disease. Although the observed response was comparable to that of other agents administered in this disease setting, the prespecified efficacy end point was not met. There were also safety concerns regarding grade 3–5 treatment-related adverse events, which occurred in 26 patients (16%), including three treatment-related deaths.[84]

Several prospective trials have been reported or are ongoing in the BCG-unresponsive space for high-risk NMIBC. In a pivotal phase 3 clinical trial involving 151 patients with BCG-unresponsive NMIBC, intravesical nadofaragene firadenovec (a gene therapy that delivers human interferon α2b complementary DNA to the tumor site, eliciting antitumor biologic responses) resulted in a 5-year OS rate of 80% and a cystectomy-free survival rate of 49%.[86–88] These results led to FDA approval. The BOND-003 trial (ClinicalTrials.gov identifier NCT04452591) of intravesical cretostimogene grenadenorepvec (an oncolytic adenovirus that acts by selectively infecting and replicating in bladder cancer cells that have alterations in the retinoblastoma pathway) is evaluating an alternative adenoviral vector-based gene therapy for the treatment of patients with BCG-unresponsive, high-risk NMIBC.[89] Preliminary results from 112 patients indicated a CRR of 75.2%. Notably, no grade 3 or greater treatment-related adverse events or deaths were reported. This study is expected to reach completion by 2029.[89] The LEGEND trial (ClinicalTrials.gov identifier NCT04752722) is evaluating detalimogene voraplasmid (EG-70), a nonviral gene therapy that acts by eliciting a local immune response at the tumor site, in patients with BCG-unresponsive disease.[90] An initial report of 19 patients in the phase 1 trial demonstrated no dose-limiting toxicities and a 67% CRR at 12-week assessment. A phase 2 trial is ongoing.

There is an interest in the value of combining intravesical immunotherapy agents with BCG or chemotherapy, and several trials are investigating the potential for synergy in this space. Under the assumption that PD-1/PD-L1 overexpression could be a mechanism of BCG resistance, the KEYNOTE-676 (pembrolizumab), CREST (sasanlimab), and POTOMAC (durvalumab) trials (ClinicalTrials.gov identifiers NCT03711032, NCT04165317, and NCT03528694, respectively) are evaluating whether the addition of immunotherapy can enhance the activity of BCG for patients with NMIBC who are BCG-naive.[91–93] The Alliance A031803 trial (ClinicalTrials.gov identifier NCT04164082) is evaluating intravesical gemcitabine and pembrolizumab in patients with BCG-unresponsive NMIBC, with primary end points of the 6-month complete response rate and the 18-month EFS rate for all patients.[94] In addition, Inman et al. reported a phase 1b/2 trial evaluating the safety and efficacy of atezolizumab with or without BCG in 24 patients with BCG-unresponsive, high-risk NMIBC, demonstrating a 6-month CRR of 33% without BCG, whereas the CRR was 42% in the combination group.[95] No patients experienced grade 4 or 5 adverse events.[95] In a novel approach, Hahn et al. tested three regimens of durvalumab therapy, which also acts by inhibiting PD-L1, in a multicenter phase 1 trial involving 28 patients with BCG-unresponsive NMIBC: durvalumab monotherapy (n = 3), durvalumab plus BCG (n = 13), and durvalumab plus external-beam radiation therapy (n = 12). Their study reported 3-month CRR of 33%, 85%, and 50% in these groups, respectively. One-year CRRs of 73% and 33% were observed in the durvalumab plus BCG and durvalumab plus external-beam radiation therapy groups, respectively.[96]

Yim et al. retrospectively evaluated the efficacy of sequential intravesical gemcitabine/docetaxel as a substitute for early radical cystectomy in 102 patients with BCG-unresponsive NMIBC. This sequential treatment led to 1-year and 2-year high-grade RFS rates of 65% and 49%, respectively. Only 20 patients underwent radical cystectomy at a median of 15.5 months after treatment induction.[97] Garneau et al. conducted another retrospective study assessing the oncologic outcomes of gemcitabine/docetaxel therapy in 35 patients with NMIBC who failed BCG therapy.[98] The 1-year and 2-year OS rates in that study were 85% and 60%, respectively, and the 1-year and 2-year PFS rates for patients with MIBC were 88% and 70%, respectively. Chevuru et al. conducted a retrospective study on patients with high-risk NMIBC who had failed BCG therapy and subsequently received gemcitabine/docetaxel therapy (n = 97). Those authors documented a complete response in 74% of patients at 3 months. The 1-year, 2-year, and 5-year high-grade RFS rates were 60%, 50%, and 30%, respectively, and the 5-year OS, PFS, CSS, and cystectomy-free survival rates were 64%, 82%, 91%, and 75%, respectively.[99]

Because different trials in this space focus on different clinical end points, comparisons across studies can become infeasible. The International Bladder Cancer Group recommends that clinical trials of therapies for BCG-unresponsive NMIBC designate RFS or the time to recurrence as the primary end point designate and OS, CSS, the time to progression, and toxicity as secondary end points.[100]

Need for better urine-based surveillance metrics in trial design

Currently used modalities for surveillance of patients with NMIBC include mandatory biopsies, cystoscopy, urine-based tests, or a combination of these approaches. However, invasive surveillance testing is associated with greater morbidity, reduced quality of life, and higher financial burden.[101–103] In a cystoscopic surveillance feasibility trial involving 45 patients with low-risk and low-risk/intermediate-risk NMIBC, low-frequency and high-frequency surveillance regimens resulted in similar levels of patient-reported quality of life and procedure-related discomfort. However, patient-reported out-of-pocket expenses were nearly three-fold higher in the high-frequency surveillance group than those in the low-frequency surveillance group.[102] There has also been a general increase in the annual cost of surveillance among patients with low-grade Ta NMIBC over time.[103]

In addition to the rising financial burden of surveillance testing, over testing beyond what is recommended by clinical guidelines is also reported. Urologic surgeons often advocate for mandatory biopsies when designing clinical trials for NMIBC because of variations in cystoscopic assessments between urologists and insufficient sensitivity of urine cytology metrics.[104] Meanwhile, a cohort study of 13,054 patients with low-grade Ta NMIBC reported significant increases in both cystoscopic surveillance and urine cytologic testing over the study period (2004–2013), hinting at overuse of testing during surveillance.[103] Thus better urine-based toxicity metrics are needed to decrease the need for invasive surveillance procedures, reduce morbidity, and improve the quality of life for all patients.

Some studies provide a positive outlook in this regard. For example, a prospective, multi-institutional study assessed the efficacy of Cxbladder Monitor (CxM), an at-home urine-based messenger RNA detection kit to identify recurrent NMIBC, in 92 patients. The study indicated that patients who tested negative with CxM ($N = 66$) did not have any recurrent disease when they underwent cystoscopy, whereas greater than 33% of patients who tested positive with CxM experienced disease recurrence.[105] Such tests can reduce the need for invasive surveillance in eligible patients, thereby decreasing surveillance-related morbidity and costs.

Understanding risk better through variant histology

Variant histology in bladder cancer is more frequently reported now, accounting for over 25% of reported cases.[106,107] The presence of variant histology in patients with NMIBC is a high-risk feature, often associated with upstaging and poor survival outcomes.[108,109] Thus knowledge of variant histology can help understand patient risk and prognosis better. In a retrospective evaluation of 8920 patients who had variant histology NMIBC, Dursun et al. observed that patients with sarcomatoid, squamous, glandular, and neuroendocrine variants had significantly higher ($p < .05$) 5-year OS rates after radical cystectomy (31.9%, 39.7%, 44.0%, and 31.0%, respectively) compared with the rates after bladder-preservation therapies (23.3%, 19.9%, 41.0%, and 21.7%, respectively). In addition, radical cystectomy did not offer a 5-year OS benefit over bladder-preservation therapies (43.9% vs. 53.2%; $p = .14$) in patients with micropapillary variants.[106]

Similarly, Miyake et al. conducted a retrospective analysis of 1490 patients with high-grade T1 NMIBC who had received intravesical BCG treatment. That study made a distinction between *variant morphology* (including nested, microcystic, micropapillary, lymphoepithelioma-like, plasmacytoid/signet ring cell/diffuse, sarcomatoid, giant cell, poorly differentiated, lipid-rich, and glycogen-rich variants) and *divergent differentiation* (including squamous, glandular, and trophoblastic differentiation), reporting variant morphology in 30 patients (2.0%) and divergent differentiation in 65 patients (4.4%). Variant morphology and divergent differentiation were not significantly associated with bladder recurrence after BCG initiation. However, patients who had variant morphology and divergent differentiation NMIBC were more likely to have a poor prognosis for cancer-specific death compared with those who had pure urothelial carcinoma ($p < .01$). Specifically, variant morphology, but not divergent differentiation, independently predicted cancer-specific death after BCG initiation (HR, 3.89; 95% CI, 1.55–9.77).[110]

Bladder-sparing protocols and trimodal therapy in the context of NMIBC

Radical cystectomy, although it is effective in the treatment of high-risk NMIBC, has a high rate of perioperative complications and can be associated with decreased quality of life.[111] Thus bladder-preserving protocols, including trimodal therapy, are being investigated.

McElree et al. reported the outcomes of a bladder-preserving protocol for 26 patients (24 bladder tumors and seven upper tract tumors) with high-risk, docetaxel-unresponsive NMIBC. This protocol involved sequential intravesical administration of gemcitabine and cabazitaxel with intravenous administration of pembrolizumab. Although 23% of patients did not continue maintenance therapy because of adverse events, 77% and 52% of treated tumors maintained a complete response at 1 and 2 years, respectively. The OS rate was 96% and 91% at 1 and 2 years, respectively, and the CSS rate was 96% at 2 years.[112] Tan et al. retrospectively investigated the survival outcomes of bladder-sparing treatment in patients with BCG-unresponsive NMIBC ($n = 114$). Thirty-eight patients underwent early radical cystectomy, and 76 received bladder-sparing treatment. The results demonstrated that the OS and CSS rates were statistically similar ($p = .4$ and $p = .9$, respectively) between patients who had

received early radical cystectomy and bladder-sparing treatment.[113] Dahl et al. reported the outcomes of the RTOG 0926 phase 2 clinical trial of a trimodal treatment in 34 patients with high-grade T1 bladder cancer who had failed BCG treatment. The trimodal therapy administered in that study comprised radiation, radiosensitizing chemotherapy with cisplatin or mitomycin/5-fluorouracil, and subsequent repeated TURBT.[114] The trial demonstrated that trimodal therapy is an effective substitute for radical cystectomy, achieving a 3-year cystectomy-free survival rate of 88% and 3-year and 5-year OS rates of 69% and 56%, respectively.[114] Overall, the use of trimodal therapy to alleviate the morbidities associated with radical cystectomy will depend on a specific selection process that weighs the individualized risks and benefits for the patient.

Cystectomy considerations and improved recovery protocols

Role and extent of lymph node dissection

The Southwest Oncology Group SWOG S1011 phase 3 trial compared standard versus extended lymphadenectomy in patients with localized MIBC undergoing radical cystectomy (n = 618; 300 patients were randomized to standard lymphadenectomy and 292 patients to extended lymphadenectomy). The study indicated that patients who received extended lymphadenectomy were more likely to experience grade 3–4 adverse events (16%) than those who underwent standard lymphadenectomy (8%). Mortality within 90 days of radical cystectomy was also higher in the extended lymphadenectomy group (16 of 292 patients) than in the standard lymphadenectomy group (nine of 300 patients). Moreover, extended lymphadenectomy was not associated with improved DFS or OS rates over the standard approach.[115] These results add to the previous LEA AUO AB 25/02 trial (ClinicalTrials.gov identifier NCT01215071), which also demonstrated no survival advantage between an extended and limited lymphadenectomy, although their patients were in a lower risk group that included those with NMIBC and excluded NAC.[116]

Notably, a recent meta-analysis of six studies (n = 2824 patients) demonstrated the previously held belief that there is a significant RFS benefit offered by extended lymphadenectomy over the standard approach (HR, 0.66; $p < .001$).[117] Furthermore, the S1011 trial excluded patients with N3 disease; and, if suspicious nodes were identified at the time of surgery and confirmed to be positive by frozen section, then those patients were also removed from the study. In addition, the trial was powered to detect a substantial 10% difference in DFS based on the extent of lymphadenectomy. Extended lymphadenectomy may still play a role in improving RFS in selected patient populations with high-risk disease and an elevated recurrence rate. However, physicians should always weigh this benefit against the reported complication rates of the extended approach as well as some studies that reported no improvement in outcomes.

Cystectomy considerations for female patients

Typically, reproductive-organ-sparing cystectomy is only indicated in patients with a single, organ-confined tumor (≤T2b) that does not involve the bladder neck or trigone (Figure 1).[118,119] Studies specifically in investigating treatments in female patients indicate that reproductive organ–sparing cystectomy may be safe in higher risk/higher stage patients without compromising cure. In a retrospective, single-institution review of 186 female patients with MIBC who underwent radical cystectomy, Bree et al. observed that 158 patients (85%) had undergone reproductive organ removal (vagina, fallopian

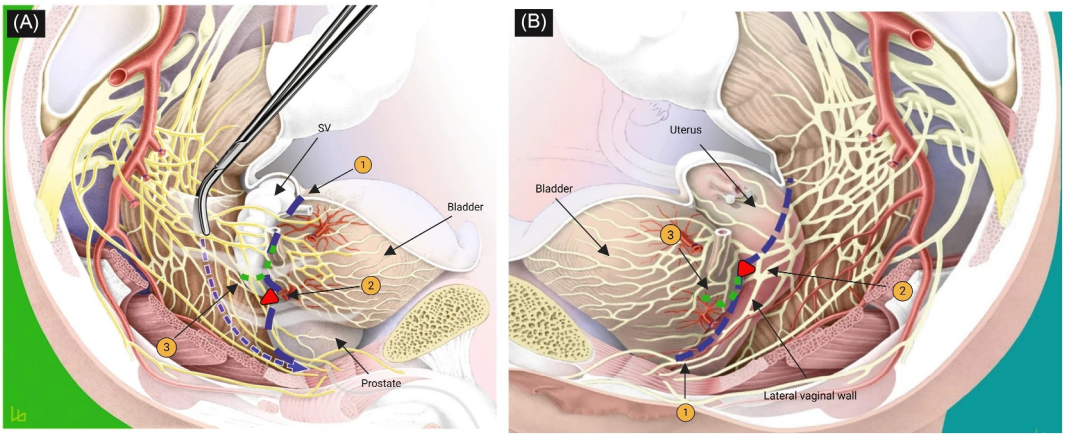

FIGURE 1 (A) Pelvic anatomic dissection model in a male patient with clamp along wide-resection plane: (1) Anatomic plane between the dorsal bladder, dorsal prostate, and anterior seminal vesicles. Dissection in this plane must be precise to avoid injury to the neurovascular bundle crossing lateral to the prostate. (2) Critical anatomic angle between the bladder wall, seminal vesicle, and base of the prostate. (3) The dissection of the plane ventral to the seminal vesicle must avoid injury to the neurovascular pelvic plexus located dorsolateral to the seminal vesicle. SV indicates seminal vesicle. (B) Pelvic anatomic dissection model in a female patient: (1) Anatomic plane between the dorsal bladder and anterior uterocervical wall. Dissection in this plane must be precise to avoid injury to the neurovascular bundle crossing ventrolateral to the paravaginal space. (2) Critical anatomic angle between the trigone, lateral vaginal wall, and cervix uteri. (3) Dissection path carried along the ventrolateral paravaginal plane (modified from Studer 2015[119]).

tubes/ovaries, uterus) during the procedure. However, only nine of 158 patients (5.7%) had any reproductive organ involvement at the time of radical cystectomy.[120] Patel et al. conducted a similar retrospective analysis involving 289 female patients with urothelial cancer, including MIBC and NMIBC, covering a broad range of tumor stages and variant histology. Of these, 188 patients underwent reproductive organ–sparing cystectomy. The reproductive organ–sparing procedure had no significant effect on positive surgical margin rates (4.3% vs. 7.9% in nonorgan–sparing cases; $p = .19$), RFS (26.1 vs. 15.3 months in nonorgan–sparing cases; $p = .94$), CSS (36.3 vs. 28.6 months in nonorgan–sparing cases; $p = .76$), or OS (25.8 vs. 23.8 months for nonorgan–sparing cases; $p = .5$).[118] These studies underscore the feasibility of reproductive organ–sparing approaches irrespective of disease stage and variant histology in female patients undergoing radical cystectomy. Despite these data, a cross-sectional survey in 2023 of 101 Society of Urologic Oncology (SUO) members revealed a significant lack of adoption of reproductive organ–sparing and neurovascular bundle–preserving radical cystectomy practices in both premenopausal and postmenopausal females with clinically localized MIBC or BCG-unresponsive NMIBC.[121] With the historically low rates of reproductive organ–sparing surgery, data on fertility and pregnancy after radical cystectomy for bladder cancer are limited to case reports/series.[122] In a retrospective study surveying female patients who had undergone radical cystectomy ($n = 22$), it was reported that 12 of 22 patients (54.5%) had not received any preoperative counseling for the changes that could occur in sexual function after the procedure, whereas six of 22 patients (27.3%) were not satisfied with the counseling they did receive.[123] Moreover, vaginal preservation was ranked as moderate to very important for 17 of 22 female patients (77.3%).[123]

A separate cross-sectional survey of 140 SUO members indicated that the odds of urologists not providing routine sexual health/dysfunction–related counseling to female patients undergoing radical cystectomy were significantly greater than those for male patients.[124] Notably, the counseling topics investigated were baseline sexual activity (20.6% vs. 9.7% for female vs. male patients, respectively; $p = .04$), baseline sexual dysfunction (60.8% vs. 20.2% for female vs. male patients, respectively; $p < .05$), risk of sexual dysfunction after radical cystectomy (20.0% vs. 6.5% for female vs. male patients, respectively; $p = .006$), possibility of nerve-preserving radical cystectomy (70.8% vs. 35.5% for female vs. male patients, respectively; $p = .002$), and postoperative sexual health/dysfunction (42.6% vs. 21.1% for female vs. male patients, respectively; $p = .01$).[124]

A qualitative study exploring women's perceptions and experiences of sexual health after radical cystectomy identified four key points: (1) Patients reported receiving little to no information from providers regarding sexual dysfunction, (2) many women were no longer sexually active postoperatively because of physical and psychological barriers, (3) those who attempted sexual activity found it disappointing because it did not feel the same as before surgery, and (4) some women noted that physical therapy helped them regain the strength to re-engage in sexual activity.[125]

These findings highlight a persistent gap in counseling and addressing quality-of-life and sexual health concerns among female patients, underscoring the need for better support and education in this area. We recommend a baseline assessment of sexual health with a validated questionnaire (e.g., the Female Sexual Function Index), extensive perioperative patient counseling to set expectations, nerve-sparing and organ-sparing surgical approaches when feasible, and follow-up assessments with administration of patient-centered resources, such as those available from the Bladder Cancer Advocacy Network. In cases where the reproductive organ–sparing approach is not feasible, vaginal reconstruction may be offered to eligible patients to overcome sexual dysfunction associated with radical cystectomy.[126] These encompass the use of bowel or skin grafts to reconstruct pelvic organs. Although the former provides a good vascular supply, it is associated with excessive mucus production (≥250 mL/day) and, as such, can be an unattractive option for some patients.[127] Conversely, a myocutaneous flap has been described as the preferred technique because it provides good cutaneous sensitivity, sufficient skin for reconstruction, and adequate vascularization.[128]

Cystectomy considerations for geriatric patients

Bladder cancer disproportionately affects the elderly population, with median ages at diagnosis and death of 73 and 79 years, respectively.[129] Patients who are older and/or unmarried are also at greater risk of suicide after radical cystectomy.[130] A retrospective analysis of 62 patients aged 70 years and older with localized MIBC who underwent geriatric assessment before undergoing radical cystectomy demonstrated that 45 patients (73%) suffered one or more complications within 30 days of the procedure. Of these, 22 patients (49%) had grade 3–5 complications, which led to death in three patients (4%).[131] This mortality rate was nearly twice the 2%–3% rate observed in all-age population studies.[131] However, a retrospective analysis conducted by Galetti et al. suggests that chronological age should not be a reason to disqualify geriatric patients from open radical cystectomy. Their study assessed 413 patients (128 were aged 75 years or older) with MIBC. Multivariate analysis indicated that OS and CSS rates did not differ significantly between patients younger than 75 years and those aged 75 years and older, although a log-rank test indicated that these survival rates were significantly higher for patients younger than 75 years ($p < .0001$ for OS; $p = .013$ for CSS). However, the age-adjusted Charlson comorbidity index was significantly greater for patients aged 75 years and older than for those younger than 75 years (5 vs. 3, respectively; $p < .0001$). This index was positively associated with the risk of early complications after open radical cystectomy in both univariate and multivariate analyses ($p = .015$ and $p = .002$, respectively).[132]

Comprehensive geriatric assessment is a multidomain evaluation of a patient's comorbidities, functional status, cognition, psychological status, nutritional status, and polypharmacy.[133] This assessment has been identified as feasible for patients and helpful in detecting vulnerabilities that facilitate patient-specific referrals and

interventions.[134] Letica-Kriegel et al. tested a pilot perioperative geriatric co-management program for patients aged 75 years and older who had undergone radical cystectomy for bladder cancer. None of the 59 patients who participated in the pilot program experienced delays in cystectomy because of logistical issues with geriatric evaluation. Two patients rescheduled their surgeries to accommodate additional workups recommended upon geriatric assessment. About 61% of the patients were visited by the geriatric service on every postoperative day, excluding the discharge day. Overall, this study highlights the feasibility of a geriatric co-management program for perioperative support and assessment.[135]

Beyond the variables of age at surgery or CCI, preoperative frailty assessments, e.g. the Fried Frailty Phenotype, Clinical Frailty Scale, or timed *up and go* tests, can enhance patient selection for radical surgery or bladder-sparing approaches. Burg et al. prospectively evaluated frailty using the Fried Frailty Phenotype in 123 elderly patients undergoing radical cystectomy and found that intermediate or high frailty scores significantly predicted postoperative complications at both 30 and 90 days. Specifically, frailty components, such as shrinking and reduced physical activity, were independently associated with the occurrence of said complications.[136] McIsaac et al. conducted a randomized controlled trial (ClinicalTrials.gov identifier NCT02934230) evaluating the effectiveness of a home-based prehabilitation program, including exercise and nutritional guidance, in older frail adults undergoing cancer surgery. The primary outcome was the 6-minute walk test distance at the first postoperative clinic visit. Overall, this intervention did not significantly improve postoperative functional recovery compared with standard care. However, a subgroup analysis demonstrated that greater adherence (≥80%) to the prehabilitation program was associated with improvements in physical function, fewer complications, and reduced disability after surgery.[137]

Frailty measures provide nuanced insights into a patient's physiologic reserve, more accurately predicting surgical morbidity and postoperative recovery. In addition, evidence increasingly supports prehabilitation programs, typically ranging from 3 to 6 weeks, to optimize surgical outcomes.[138] Prehabilitation, combining nutritional optimization, physical exercise, and psychosocial interventions, appears most beneficial in elderly or frail patients, substantially reducing perioperative complications and length of hospital stay. Tailoring these interventions through multidisciplinary input helps maximize benefits and guides appropriate selection of candidates for radical cystectomy or bladder preservation.

Enhanced recovery after surgery protocols for cystectomy

Enhanced recovery after surgery (ERAS) protocols aim to facilitate evidence-based improvements in the perioperative care and health outcomes of patients undergoing surgery by targeting: (1) preoperative care areas, such as preoperative education and counseling, risk stratification and optimization of comorbidities, and nutrition and smoking-cessation advice; (2) intraoperative care areas, such as standard anesthetic protocol, use of alvimopan, limiting opiate use, intraoperative fluid management, and minimally invasive technique; and (3) postoperative care areas, such as postoperative diet, limiting opiate use, postoperative analgesia, and early mobilization.[139] For patients undergoing cystectomy, randomized controlled trials have demonstrated the efficacy of ERAS protocols in significantly reducing postoperative complications, time to flatulence, time to first bowel movement, time to regular diet, and length of hospital stay.[140–142] Similar trends were observed in a retrospective study comparing outcomes in patients with bladder cancer who underwent open radical cystectomy in pre-ERAS ($n = 36$) versus post-ERAS ($n = 37$) time periods.[143] This study reported significant reductions in various postsurgery outcomes in post-ERAS patients compared with the pre-ERAS group, such as length of hospital stay (7 vs. 12 days, respectively; $p = .003$), time to flatulence (3 vs. 4 days, respectively; $p = .001$), time to bowel function recovery (5 vs. 7.5 days, respectively; $p = .016$), and total parenteral nutrition requirement (1 vs. 8 days, respectively; $p = .014$). However, no significant differences were observed in postoperative complication rates in the pre-ERAS and post-ERAS groups within 90 days of the procedure ($p > .05$).[143]

Another retrospective analysis of 2111 patients with primary urothelial bladder cancer, of whom 967 (46%) were in the ERAS group for radical cystectomy, also demonstrated a significant reduction in the length of hospital stay with the ERAS regimen ($p < .001$).[144] Univariate analysis indicated that OS rates at 1, 3, and 5 years were significantly improved in the ERAS group (86%, 73%, and 67%, respectively) compared with the non-ERAS group (84%, 68%, and 59.5%, respectively; $p = .002$). On multivariate analysis, no significant differences were noted in OS or RFS rates ($p = .28$ and $p = .75$, respectively) between the ERAS and non-ERAS groups. Thus long-term oncologic outcomes were not significantly influenced by ERAS protocol implementation in this study.[144] Crettenand et al. found that ERAS protocols had the potential to affect long-term oncologic outcomes. Their single-center, prospective study included 107 patients with urothelial carcinoma of the bladder (MIBC or treatment-refractory NMIBC) who underwent open radical cystectomy with bilateral pelvic lymph node dissection. Seventy-four (69%) of the patients were in ERAS group. The length of hospital stay, although shorter in the ERAS group than in the pre-ERAS group, was not statistically different ($p = .06$). The 30-day rate of major complications was significantly greater in the ERAS group (26%) than in the pre-ERAS group (12%; $p = .01$). Even so, the 5-year OS and CCS rates of patients in the ERAS group (67% and 74%, respectively) were significantly higher than in the pre-ERAS group (36% and 48%, respectively; $p = .003$ and $p = .02$, respectively).[145]

Briggs et al. performed a scoping review of randomized controlled trials that assessed nontherapeutic and outpatient prehabilitation/rehabilitation programs, including prehabilitative/rehabilitative exercise, nutrition, and psychological support, for patients with bladder cancer. Although their review excluded ERAS protocols, it included their outpatient components. The study reported a statistically significant positive impact of psychological support (including cognitive

behavioral therapy and smoking and alcohol cessation), preoperative and postoperative exercise, nutritional support, and patient stoma education on the quality of life of patients with bladder cancer.[146] Overall, there is a need for prospective and controlled studies evaluating the impact of ERAS protocols on surgical outcomes in patients undergoing radical cystectomy for bladder cancer.

ADVANCES IN UPPER TRACT UROTHELIAL CARCINOMA

Although UTUC and UCB share histologic similarities, there are clinical differences in embryologic cellular origin, genomic landscape, etiology, demographics, and anatomic aspects that bear on disease biology and management. Compared with UCB, UTUC is typically more invasive at presentation and has a worse overall prognosis. Demographically, there is a lower male predominance and a strong association with causative factors from Lynch syndrome and toxic exposures, such as aristolochic acid or birthwort. There are also distinct genomic differences between the two, such as a higher frequency of *FGFR3* and *HRAS* mutations, and a lower frequency of *TP53* and *RB1* mutations in UTUC. These genomic and clinical differences, as well as the risk to vital organ function in patients with UTUC, necessitate distinction of management for these vulnerable patients, as described in dedicated guidelines from the European Association of Urology and American Urological Association (AUA)/SUO, to address these unique challenges and define clinical risk categories. Renal function, in particular, is a key clinical factor because most patients with UTUC have poor baseline function, which is rendered significantly worse after surgical management. Therefore, recent studies evaluating perioperative care have focused on optimizing therapeutic approaches, including NAC/adjuvant chemotherapy and immunotherapy, as well as nephron-sparing treatments, in carefully selected patients (Table 3).

Neoadjuvant/adjuvant chemotherapy as a standard of care

The Peri-Operative Chemotherapy versus Surveillance in Upper Tract Urothelial Cancer (POUT) phase 3 trial (ClinicalTrials.gov identifier NCT01993979) explored the efficacy of adjuvant gemcitabine/platinum-based chemotherapy in improving DFS in patients with locally invasive or node-positive UTUC who had undergone radical nephroureterectomy.[147,148] This study was conducted on a UK-based cohort of 261 patients, of whom 132 were in the adjuvant chemotherapy group and 129 were in the surveillance group.[147,148] Patients were selected based on excellent baseline functional status and the presence of advanced-stage tumors (pathologic T2 or greater [≥pT2] and any lymph node status [Nany]). The 5-year DFS rate was significantly higher in the adjuvant chemotherapy group compared with the surveillance group (62% vs. 45%, respectively; HR, 0.58; $p = .004$).[149] The 5-year OS rate was also nonstatistically significantly greater in the adjuvant chemotherapy group (66% vs. 57%, respectively; HR, 0.76; $p = .17$).[149]

The major effect of renal functional loss after surgery is a compelling rationale for the use of nephrotoxic chemotherapy before nephroureterectomy, at a time when renal function is optimal and patients are better able to tolerate a full course of therapy. Cisplatin eligibility declines from approximately 58% of patients in the neoadjuvant setting to only 15% in the adjuvant setting.[150–152] Margulis et al. reported a phase 2 trial of NAC for AUA/SUO high-grade UTUC. Thirty patients who were cisplatin-eligible received dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin. The results indicated a relatively safe toxicity profile (grade 3–4 toxicity in 23% of patients; no grade 5 toxicity). A complete response (post-NAC; ypT0N0) was observed in 14% of patients, whereas a nonmuscle-invasive final pathologic stage (≤ypT1N0) was noted in 62% of patients.[153] Coleman et al. reported a larger, fully accrued, multicenter phase 2 trial of neoadjuvant split-dose gemcitabine plus cisplatin in 57 patients with AUA/SUO high-risk, unfavorable UTUC. Thirty-six patients (63%) had a defined pathologic response to the neoadjuvant therapy (≤ypT1N0), with 11 (19%) exhibiting a complete pathologic response (ypT0N0). Therapy was well tolerated, with 51 patients (89%) tolerating three or more complete treatment cycles and 27 (47%) tolerating four complete cycles. Compared with historical data from patients who underwent radical nephroureterectomy without NAC, this study indicated superior OS and PFS rates. The OS rates were 93% and 79% at 2 and 5 years, respectively, compared with 68%–84% and 29%–62%, respectively, from prior published studies without neoadjuvant therapy. In addition, the PFS rates were 89% and 72% at 2 and 5 years, respectively, compared with 50%–76% and 40%–68%, respectively. from previous studies without neoadjuvant therapy.[154]

Tae et al. compared NAC and adjuvant chemotherapy for UTUC in a South Korea–based cohort of 8705 patients who underwent radical nephroureterectomy with bladder cuff excision ($n = 6627$ underwent surgery alone; $n = 94$ received NAC; $n = 1984$ received adjuvant chemotherapy). The chemotherapy combination administered was either gemcitabine plus cisplatin or combined methotrexate, vinblastine, doxorubicin, and cisplatin. This study did not identify any significant difference in OS rates between the NAC and adjuvant chemotherapy groups, both with and without PSM adjustment ($p = .48$ and $p = .60$, respectively).[155] Importantly, the use of supportive therapies, such as blood transfusion and granulocyte-colony–stimulating factor, were significantly lower in patients who received NAC. It was not reported how patients were selected for treatment or how many patients who were platinum-eligible before surgery became ineligible after surgery because of renal functional loss or what impact this may have had on survival.

Neoadjuvant immunotherapy under evaluation

Necchi et al. conducted a feasibility study of pembrolizumab as neoadjuvant immunotherapy in 10 patients with high-risk UTUC. Pembrolizumab was not identified as effective in this setting and

TABLE 3 Perioperative studies on treatments for upper tract urothelial carcinoma (completed and ongoing trials).

Clinical trial/ NCT identifier	Condition	Location/design	Experimental intervention	Primary outcomes for evaluation	Trial status
EA8141, phase 2/ NCT02412670	High-grade UTUC	Multicenter, USA/ nonrandomized, open-label	Neoadjuvant methotrexate + vinblastine + doxorubicin + cisplatin; neoadjuvant gemcitabine + carboplatin	Pathologic CRR	Completed (2022)
10-208, phase 2/ NCT01261728	High-grade UTUC	Multicenter, USA/open-label	Neoadjuvant gemcitabine + cisplatin	Pathologic response rate	Completed (2025)
NCC2121, phase 2/ NCT04099589	MIBC; UTUC	Single-center, China/ nonrandomized, open-label	Neoadjuvant gemcitabine/cisplatin + toripalimab	Pathologic CRR	Unknown status (was estimated to be completed by October 2022)
iNDUCT, phase 2/ NCT04617756	High-risk UTUC	Multicenter, France/open-label, multicohort	Neoadjuvant gemcitabine with cisplatin or carboplatin + durvalumab	Pathologic CRR	Ongoing (recruiting)
PURE-02, feasibility study/ NCT02736266	High-grade UTUC	Single-center, Italy/open-label	Neoadjuvant pembrolizumab	Postradical nephroureterectomy pathologic response rate; surgical and medical safety; feasibility	Completed (2022)
POUT, phase 3/ NCT01993979	Locally invasive or node-positive UTUC	Multicenter, UK/randomized, open-label	Adjuvant gemcitabine + platinum-based chemotherapy (cisplatin or carboplatin)	3-year DFS	Unknown status (was estimated to be completed by May 2022)
ENLIGHTED, phase 3/ NCT04620239	New or recurrent, low-grade, noninvasive UTUC	Multicenter, global/ nonrandomized, open-label	Nephron-sparing padeliporfin VTP	CRR (no UTUC tumors in ipsilateral calyces, renal pelvis, or ureters)	Ongoing (recruiting)
OLYMPUS, phase 3/ NCT02793128	Low-grade, noninvasive UTUC	Multicenter, USA and Israel/ open-label	Nephron-sparing mitomycin	CRR	Completed (2020)

Abbreviations: CRR, complete response rate; DFS, disease-free survival; MIBC, muscle-invasive bladder cancer; UTUC, upper tract urothelial carcinoma; VTP, vascular-targeted photodynamic therapy.

resulted in one incidence of treatment-related mortality, two cases of disease progression necessitating preoperative chemotherapy, and only one major clinical response.[156]

Bi et al. reported promising preliminary results from a phase 2 trial of combined gemcitabine/cisplatin and toripalimab as a neoadjuvant regimen in patients with UTUC.[157] Of the 15 patients who were analyzed, three (20%) had a complete pathologic response, whereas all (100%) experienced disease control. No grade 5 adverse events related to chemotherapy or immunotherapy were reported, and all patients were alive and tumor-free at follow-up (median follow-up, 25.6 months).[157] An ongoing phase 2 trial is evaluating gemcitabine with cisplatin or carboplatin and durvalumab as a neoadjuvant therapy in high-risk patients with UTUC.[158]

Nephron-sparing treatment options

Several nephron-sparing treatment protocols are available for patients who have an imperative indication or when nephroureterectomy may qualify as overtreatment and disease-related mortality and patient safety are not anticipated to be compromised. Endoscopic approaches involve using lasers, either alone or in combination with other techniques, to vaporize or coagulate tumor tissues.[159] Such techniques, although organ-sparing, are often associated with high recurrence rates. Hoffman et al. conducted a case–control study retrospectively evaluating patients with low-grade UTUC who received nephron-sparing endoscopic treatment (n = 25) versus nephroureterectomy (n = 23).[160] The nephron-sparing treatment involved a combination of ureteroscopic laser treatment and

monopolar electrocautery. Notably, the nephron-sparing treatment group had no disease-related mortality in the follow-up period, whereas the nephroureterectomy group had one disease-related death. However, the nephron-sparing approach had a higher rate of recurrence in the bladder and ureters (44% and 36%, respectively). A rigorous follow-up protocol is necessary with nephron-sparing treatments because multiple endoscopic procedures may be required to resolve recurrence.[160,161]

Vascular-targeted photodynamic therapy (VTP), another endoscopic technique, involves light-mediated activation of a photosensitizing drug for targeted endoluminal treatment of cancers, including UTUC.[162,163] Yip et al. conducted an open-label phase 1 study to evaluate the safety and efficacy of the photosensitizing drug padeliporfin, which was administered intravenously and activated by near-infrared light (753 nm) delivered to tumor sites in the collecting system through an optic fiber. This study included 19 patients who had residual or recurrent UTUC after previous endoscopic treatment. VTP resulted in a tumor response in 94% of patients, with a complete response (no visible tumor, no malignant cells detected by urine cytology) noted in 50% of patients, more commonly in patients who had low-grade tumors or tumors <15 mm. The treatment was identified as generally safe, with preserved kidneys at the 6-month follow-up and no adverse event resulting in study discontinuation.[163] This study was followed with a multicenter phase 3 trial (ENLIGHTED; ClinicalTrials.gov identifier NCT04620239) of padeliporfin VTP for patients who had two or fewer low-grade UTUC tumors, with the largest tumor measuring ≤15 mm in the kidney and ≤20 mm in the ureter. Although enrolment in the trial is ongoing, 17 patients had been treated as of January 2024.[164] VTP was able to achieve a complete response in 77% of the treated patients and a partial response in the rest. Preliminary safety data were consistent with the results of the phase 1 study.[163,164]

A separate nephron-sparing treatment for UTUC received FDA approval in 2020.[165] This mitomycin C-containing reverse-thermal gel, which changes its state from liquid at low temperatures to a gel at body temperature, provides sustained delivery of the therapeutic to the tumor regions for 4–6 hours.[165] The single-arm phase 3 trial (OLYMPUS; ClinicalTrials.gov identifier NCT02793128) in 71 patients with low-grade UTUC reported a complete response in 59% of the patients who received induction therapy (six weekly treatments).[166,167] At the 12-month follow-up, 56% of the patients who had a complete response had a maintained response, and 20% had disease recurrence, leading to an overall 12-month Kaplan-Meier durability of 82%.[166]

Genomic and Lynch syndrome-related considerations

High rates of *FGFR3* mutations have been reported in UTUC.[168,169] This raises the possibility of using FGFR3 inhibition as a novel treatment strategy. In a phase 1b trial of FGFR3 inhibition as a treatment approach, nine of 14 enrolled patients with localized UTUC had *FGFR3* mutations.[170] Six of the nine patients with *FGFR3*-mutant UTUC responded to FGFR3 inhibition, with a median tumor size reduction of 67% (range, 25%–88% reduction). Moreover, three of five responders for whom radical nephroureterectomy had been indicated initially were able to undergo endoscopic management after FGFR3 inhibition therapy.[170] The PROOF 302 phase 3 trial (ClinicalTrials.gov identifier NCT04197986) aimed to evaluate infigratinib (BGJ398) as adjuvant therapy in patients with invasive urothelial carcinoma (UTUC and UCB), but the study was stopped early by its sponsor because of a lack of accrual.[169]

Lynch syndrome, or hereditary nonpolyposis colorectal cancer, is an autosomal-dominant genetic disease that predisposes patients to various cancers.[171–173] UTUC is the third most common among these Lynch syndrome–related cancers, affecting up to 28% of patients with Lynch syndrome.[172,173] Compared with the general population, the risk of developing UTUC is 14-fold higher in patients with Lynch syndrome.[173,174] Patients with Lynch syndrome–associated UTUC are typically younger than others with UTUC, and they are more likely to be female.[172] The European Association of Urology recommends that patients with UTUC who are younger than 65 years or have a family history of Lynch syndrome–associated cancers should undergo molecular and genetic testing for Lynch syndrome diagnosis.[174] Patients with Lynch syndrome who are aged 45–50 years should be systematically screened for UTUC with annual urinalysis, urinary cytology, and biannual abdominal ultrasound.[174]

Doudt et al. retrospectively evaluated the efficacy of ICI therapy in 10 patients with Lynch syndrome–associated UTUC (six with metastatic disease and four with localized disease). The CRR was 75% (three of four patients) in localized cases, whereas the 2-year PFS rate was 67% (four of six patients) in metastatic cases.[175] However, prospective studies assessing the efficacy of ICI in Lynch syndrome–associated UTUC are still needed.

Understanding the impact of variant histology on cancer risk

Compared with UCB, the impact of variant histology on the prognosis of patients with UTUC is relatively less studied.[176,177] Recent studies on variant histology have improved our understanding of the risks of high-grade and high-stage disease, recurrence, and mortality in patients with UTUC. Nogueira et al. retrospectively analyzed clinical data from 705 patients with UTUC who had undergone nephroureterectomy, of whom 47 patients (6.7%) had variant histology. Notably, variant histology was significantly associated with higher T stage ($p < .001$) on final pathology, worse CSS (HR, 2.14; $p = .002$), and worse OS (HR, 1.74; $p = .008$).[176] Similar observations were made in another retrospective analysis, in which 70 of 687 patients (10.2%) with UTUC who had undergone radical nephroureterectomy had variant histology.[177] In that study, variant histology was significantly associated with higher grade and pathologic T stage at diagnosis ($p = .01$ and $p = .02$, respectively), positive surgical margins, and lymphovascular invasion ($p < .0001$ for both).[177] These trends mirror

the results of a retrospective study by Takemoto et al. conducted on 223 patients with UTUC who underwent radical nephroureterectomy. Thirty-two of those patients (14.3%) had variant histology, which was significantly correlated with tumor grade (grade 3), pathologic T stage (≥pT3), and lymphovascular invasion ($p < .01$ for all). Interestingly, even on multivariate analysis, variant histology was identified as significantly associated with poorer CSS (HR, 2.36; $p = .014$) and OS (HR, 2.07; $p = .014$). In fact, the authors were able to use variant histology, in combination with lymphovascular invasion, to risk-stratify patients and discover significant differences in PFS, CSS, and OS rates among three different risk categories (low, intermediate, and high).[178]

Other studies have investigated risk-stratification strategies for UTUC.[179,180] Miyake et al. used Japanese Nishinihon Uro-Oncology Extensive Collaboration Group scores to risk stratify patients with UTUC into four groups (low, intermediate, high, and highest risk). The authors also developed site-specific risk models for renal pelvic and ureteral urothelial carcinoma. Among 1917 patients with UTUC who underwent radical nephroureterectomy, 1307 were included in the model-development data set, and the remaining 610 patients were included in the external validation data set. Of note, postoperative extra-urinary tract recurrence and cancer-specific death predicted by the site-specific risk models were closely correlated with real-world observations in the validation data set.[180] Foerster et al. created a risk-stratification model to identify low-risk patients with UTUC who may be well suited for nephron-sparing endoscopic surgery. Their retrospective study evaluated 1214 patients with nonmetastatic UTUC who underwent radical nephroureterectomy. Of these, 659 patients (54.3%) had ≤pT1N0/Nx disease, and 555 had ≥pT2/N-positive disease. The developed risk-stratification model had a predictive accuracy (AUC-receiver operating curve analysis) of 75%, which was greater than the 66%–71% accuracy achieved with existing models.[179]

CONCLUSIONS

UCB and UTUC are distinct clinical entities, each harboring specific diagnostic, treatment, and prognostic recommendations. Regardless of disease location, risk-stratification tools and a multidisciplinary approach should be used to determine the therapeutic approach for any given patient, prioritizing an individualized assessment of risks and benefits. When feasible, organ-preserving modalities should be pursued, specifically in vulnerable populations at risk of overtreatment. Multidisciplinary programs are encouraged to deliver the best care for patients with UCB and UTUC.

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