Review

A narrative review of advances in the management of urothelial cancer: Diagnostics and treatments

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Abstract

Urothelial carcinoma (UC) refers to the malignancies originating from transitional epithelium located on the upper and lower urinary tract. Precise diagnosis of UC is crucial since it dictates the treatment efficacy and prognosis of UC patients. Conventional diagnostic approaches of UC mainly fall into four types, including liquid biopsy, imaging examination, endoscopic examination, and histopathological assessment, among others, each of them has contributed to a more accurate diagnosis of the condition. Therapeutically, UC is primarily managed through surgical intervention. In recent years, minimally invasive surgery (MIS) has been incrementally used and is showing superiority in terms of lowered perioperative morbidity and quicker recovery with similar oncological outcomes achieved. For advanced UC (aUC), medical therapy is dominant. While platinum-based chemotherapies are the standard first-line option for aUC, some novel treatment alternatives have recently been introduced, such as immune checkpoint inhibitors (ICIs), targeted therapies, and antibody-drug conjugates (ADCs). ADCs, a group of sophisticated biopharmaceutical agents consisting of monoclonal antibodies, cytotoxic payload, and linker, have been increasingly drawing the attention of clinicians. In this review, we synthesize the recent developments in the precise diagnosis of UC and provide an overview of the treatment options available, including MIS for UC and emerging medications, especially ADCs of aUC.

Keywords: Diagnosis, Immunoconjugates, Surgery, Therapy, Urethral neoplasms, Urinary bladder neoplasm

1. PRECISE DIAGNOSIS OF UROTHELIAL CANCER

Urothelial carcinoma (UC) represents a spectrum of malignancies of the upper and lower urinary tracts. Upper tract UC (UTUC) originates from the renal pelvis, and ureter, and UC from lower urinary tracts can be derived from the bladder or urethra. Bladder cancer (BC) includes most cases of UC and is divided into two categories, that is, muscle-invasive BC (MIBC) and non-MIBC (NMIBC). Other UC, such as UTUC, can also be classified as muscle-invasive and non-muscle-invasive, with the former accounting for 50 – 60% of overall cases. Clinically, the challenges of UC diagnosis are multifaced, including its asymptomatic onset at early stages, shared symptoms with other non-neoplastic urinary conditions, the invasiveness of diagnostic procedures, and

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Received: 28 May 2024; Revision received: 16 July 2024; Accepted: 22 July 2024; Published: 16 August 2024

How to cite this article: Wu S, Xiong S, Li J, *et al.* A narrative review of advances in the management of urothelial cancer: Diagnostics and treatments. *Bladder.* 2024;11(1):e21200003. doi: 10.14440/bladder.2024.0003

the high recurrence rates following initial treatment. Such intricacies escalate the importance of a precise diagnosis. Early detection of UC with high accuracy can avoid delay in treatment, contributing to more favorable outcomes. Moreover, precise diagnosis in terms of specific grades and stages allows for personalized treatment, more accurate prognostication, and improved therapeutic efficacy. In this review, we will discuss the conventional and novel methodologies used for the accurate diagnosis of UC, with particular emphasis placed on liquid biopsy, imaging examination, endoscopic examination, and histopathological assessment (Figure 1).

1.1. Liquid biopsy

Liquid biopsy, encompassing the analysis of blood, urine, and other bodily fluids rather than tissue specimens, is emerging as a non-invasive diagnostic alternative with substantial potential. Some specimens used for UC diagnosis include circulating or urine tumor cells, cell-free DNA, cell-free RNA, extracellular vesicles, proteomics, and metabolomics. In clinical practice, urine cytology has been extensively used thanks to their convenience, cost-effectiveness, and high specificity [1-3]. On the other hand, urine cytology shows limited sensitivity in the detection of low-grade or early-stage UC, and the reporting rate for atypical urothelial cells remains high in spite of the introduction of the standardized diagnostic criteria, the Paris System for Reporting Urinary Cytology. Fluorescence *in situ* hybridization (FISH) can identify genetic alterations that typically precede morphological changes, and, hence, have been integrated into the arsenal of routine BC surveillance methods [4]. Studies indicated that the UroVysion FISH achieved a higher sensitivity (60-80%) compared with urine cytology for BC diagnosis, but is still of limited value when used for low-grade or small tumors [5,6]. For UTUC, the sensitivity for FISH was just roughly 50%, which substantially limits its application in clinical practice [7].

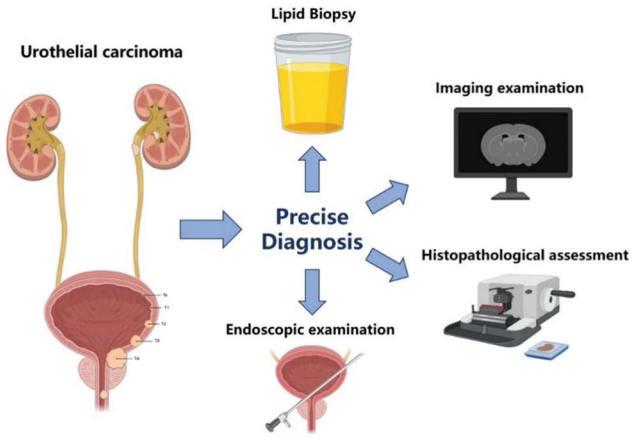

Figure 1. The precise diagnosis of urothelial carcinoma. All figures were produced with BioRender (https://app.biorender.com/).

To overcome the aforementioned weaknesses of urine cytology, artificial intelligence (AI) may be a viable solution. Wu *et al.* [8] constructed the Precision Urine Cytology AI Solution (PUCAS) using liquid-based cytology slides. The sensitivity of PUCAS ranged from 89% to 100% in retrospective and prospective validation sets, showing a superior diagnostic performance as compared with urine cytology and FISH. Besides, the PUCAS also yielded a higher sensitivity than cytology and FISH, for the diagnosis of UTUC, low-grade and early-stage tumors. DNA methylation, a principal epigenetic regulator of gene expression, is often associated with aberrant gene expression. Detection of urine DNA methylation through polymerase chain reaction (PCR) or time-of-flight mass spectrometry showed a better diagnostic performance compared with cytology and FISH, especially for the diagnosis of the early-stage, low-grade, and recurrent BC. They facilitate cancer screening, recurrence detection, and help avoid invasive cystoscopy [9-11]. Exosomes, or microvesicles, measuring between 30 and 150 nm and encompassing diverse nucleic acids such as mRNAs, miRNA, and long non-coding RNAs (lncRNAs) [12,13], present another valuable diagnostic option. Recent studies reported that the detection of lnRNA from urine exosomes including ELNAT1 and BLACAT2 showed a favorable diagnostic performance in BC patients [14,15]. To sum up, even though novel lipid biopsy methods have yet to replace traditional approaches such as cytology, they undeniably show a promising prospect toward a precise diagnosis of UC.

1.2. Imaging examination

Imaging examination represents an important means for the diagnosis of UC. Ultrasonography (US) serves as the initial and fundamental screening tool for BC, with contrast-enhanced US being able to detect BC tumor sized more than 0.5 cm at a sensitivity of 90% [16]. Although the US excels at identifying hydronephrosis and intraluminal masses within the bladder, it can not definitively rule out etiologies of hematuria [17]. Multi-detector computed tomography (CT) allows for the detection of small tumor (1~5 mm) and can determine the status of perivesical fat and adjacent organ invasion [18]. Whereas, CT is unable to differentiate tumors of stages Ta and those of T3a tumors and can hardly distinguish between inflammatory and metastatic enlarged lymph node [19]. Multiparametric magnetic resonance imaging (mpMRI) is superior to CT in terms of soft-tissue contrast resolution. Therefore, mpMRI plays an important role in the evaluation of muscle-invasiveness, with a sensitivity of 90 – 94% and a specificity of 87 – 95% [20]. Recently, the Vesical Imaging Reporting and Data System (VI-RADS) scoring system was introduced, and it provides a standardized methodology for both the acquisition and reporting of mpMRI for patients with BC [21]. Despite reports about its significant

diagnostic accuracy and good inter-reader concordance using VI-RADS, large-scale, multi-centered studies are needed for its extensive validation. For UTUC, CT urography (CTU) possesses the highest accuracy, with a study reporting a pooled sensitivity of 92% and a pooled specificity of 95% [22]. CTU can delineate tumor location, invasive depth, and the relationship of the tumor with surrounding organs. Magnetic resonance urography (MRU) is recommended for patients who cannot undergo CTU due to the contraindications related to iodinated contrast media or radiation. A study revealed that MRU achieved a sensitivity of 75% when used for diagnosing UTUC <2 cm [23].

Apart from the conventional imaging examinations as mentioned above, new imaging modalities are also drawing public attention. Positron emission tomography combined with CT or magnetic resonance imaging (PET-CT/MRI) is a functional imaging technique that simultaneously displays anatomy and metabolism, and mostly uses ^{18}F-fluorodeoxy glucose (^{18}F-FDG) as the radioactive tracer for UC diagnosis. ^{18}F-FDG can accumulate in metabolically active tissues such as tumor cells and is increasingly used for the detection of lymph node metastasis and distant metastasis in clinical practice. A study revealed that ^{18}F-FDG PET/CT showed higher sensitivity than CT/MRI for LN evaluation, with a comparable specificity achieved [24], showing its superiority to magnetic resonance imaging (MRI) and CT in the detection of LN metastasis [25-27]. Besides, a meta-analysis systematically reported that ^{18}F-FDG PET/CT could detect distant metastasis with a pooled sensitivity and specificity of 82% and 89%, respectively [28]. Except for the ^{18}F-FDG, other radioactive tracers were also used for LN metastasis detection, including ^{11}C-choline and ^{11}C-acetate [29]. The development of radiomics provides an alternative to precise diagnosis using medical imaging, as evidenced by its extensive application across a wide array of studies. Researchers extracted radiomic features from CT and MRI and constructed nomograms on the basis of the radiomic features in combination with selected clinicopathological risk factors [30]. The nomogram attained good predictive accuracy in detecting LN metastasis in BC patients, showing radiomics is superior in high-throughput extraction of medical image features.

1.3. Endoscopic examination

Cystoscopy and ureteroscopy (URS) remain the gold standard for the diagnosis of BC and UC. White light (WL) cystoscopy is considered to be the standard procedure to identify suspicious lesions in BC and has shown excellent sensitivity for the identification of papillary lesions. Whereas, flat cancerous tissue, such as carcinoma *in situ* (CIS), and small lesions, tend to go undetected. Photodynamic diagnosis (PDD) using fluorescence cystoscopy, also called blue light cystoscopy, refers to the process of intravesical instillation of photosensitizing agents, including 5-aminolaevulinic acid, hexaminolevulinate and pirarubicin [31]. Following this, porphyrins, notably protoporphyrin IX (PpIX), selectively accumulate in proliferative urothelial cells such as malignant cells, and emit red fluorescence under blue-light illumination. PDD reportedly could identify approximately 40% of CIS cases, underscoring its enhanced accuracy in detecting flat lesions compared with its WL light counterpart [32]. Narrow-band imaging (NBI) leverages specific wavelengths of filtered WL that are absorbed by hemoglobin within the vasculature of the bladder mucosa, culminating in enhanced vascular contrast (EVC) designed to delineate malignant bladder lesions marked by atypical or augmented vascularity. Researches showed that NBI could increase the detection rate of BC [33]. While, in clinical practice, the adoption of fluorescence cystoscopy and NBI remain modest due to its low specificity and expense. For UTUC, flexible URS is utilized for ascertaining the presence, characteristics, and dimensions of tumors while concurrently inspecting the ureter, renal pelvis, and collecting system [7]. Besides, URS is also performed for biopsy of suspicious lesions.

Some new technologies have been developed to enhance the accuracy of endoscopic diagnosis. To combine multiple endoscopic modalities, including blue light fluorescence, PpIX fluorescence, EVC, tissue autofluorescence, and WL imaging, Kriegmair *et al.* [34] adapted a real-time multispectral imaging (rMSI) device for urethrocystoscopic visualization of employing all five modalities simultaneously, to achieve multiparametric cystoscopy. Using rMSI setup, 31 lesions were detected, of which 27 were malignancies histopathologically validated. On a Likert scale ranging from 0 (not suspicious) to 3 (clearly suspicious), images from single modalities of malignant lesions were rated less suspicious than the MP images. The study demonstrated that the integration of endoscopic modalities improved the detection of BC. In recent years, AI has been proved to be a promising tool that can enhance the cystoscopic and ureteroscopic diagnosis [34-36]. In a study utilizing real-world cystoscopic images from multiple centers [37], the authors developed a Cystoscopy Artificial Intelligence Diagnostic System (CAIDS) for BC diagnosis using cystoscopic images under WL. The CAIDS achieved an accuracy of >97% for BC detection and outperformed urologists in terms of accuracy (accuracy = 0.939; sensitivity = 0.954) and latency (12 s). The study set a heuristic example of the application of AI in UC precise diagnosis leveraging endoscopic images.

1.4. Histopathological assessment

In clinical practice, histopathological assessment of UC can be roughly divided into two parts. For initial diagnosis,

biopsy following cystoscopy or URS is crucial, especially for the diagnosis of CIS and UTUC. For BC patients, histopathological assessment directly proceeding transurethral resection of the bladder (TURB) is recommended when BC is visualized unequivocally by imaging examinations. With MNIBC, not only can TURB provide histopathological diagnosis and staging but also resect the whole tumor for curative purpose, the former being the only objective for MIBC and metastatic cancer. Therefore, tumor resection by TURB always includes the exophytic part of the tumor, the underlying bladder wall with the detrusor muscle, and the edges of the resection area. Nevertheless, for diagnostic TURB, some dilemmas still remain. Misdiagnoses are common since specimens acquired form TURB frequently lack a full muscle layer, being fragmented and of poor quality [38-40]. Besides, for atypical cancerous lesions, precise diagnosis is still a challenge. When patients undergo subsequent treatment such as radical cystectomy (RC) or radical nephroureterectomy (RNU), specimens are postoperatively harvested and histopathologically diagnosed. The histopathological assessment clarifies the diagnosis and staging of the primary cancer and defines the status of lymph node metastasis. However, pathological diagnosis is notoriously labor-intensive, time-consuming, and experience-dependent. Besides, microchanges in the pathological slide, such as micrometastases in lymph nodes, are easily missed by the naked eyes [41]. Furthermore, it was reported that interobserver variability existed in the staging and grading of BC, suggesting that histopathological grading and staging are subject to subjective judgment [42,43]. Compared with traditional hematoxylin and eosin staining for morphological evaluation, immunohistochemistry (IHC) also detects the molecular feature of tissues. For example, GATA3, CK7, CK20, p63, HMWCK, and CK5/6 markers help determine the origin of urothelium [44]. With regard to the precise diagnosis, IHC is also instrumental for discriminating between CIS and reactive hyperplasia, pathologically diagnosing spindle-shaped cell tumor, including sarcomatoid urothelial tumors, leiomyosarcoma, and rhabdomyosarcoma, based on relevant markers [44].

Deep learning refers to the learning pattern that utilizes multiple dense layers with a large number of parameters to uncover the complex non-linear relationships behind data. Due to the high-resolution characteristics of pathological images, the superiority of deep learning in histological assessment is beyond compare. To address the aforementioned problems of TURB, researchers developed an automated analysis system, known as the pathological artificial intelligence diagnostic model (PAIDM), using whole slide images from BC patients undergoing TURB [45]. The PAIDM showed outstanding diagnostic performance in terms of determining invasion depth and histological grades at both patch and WSI levels, being non-inferior to pathologists. With the help of deep learning, by analyzing gigapixel-sized digital images and mining microscopic lesions, a lymph node metastases diagnostic model (LNMDM) performed excellently in detecting lymph node metastasis of BC, with an AUC > 0.977 [41]. Of note, in 13 patients, lymph node metastases were diagnosed by the LNMDM but were missed by pathologists, highlighting the clinical value of AI in precise histopathological diagnosis of BC. Recently, molecular stratification through the detection of genomic alterations is gaining popularity due to the inherent heterogeneity characterizing UC, especially BC. Existing molecular subtype classification systems, such as tetradic classification by the Cancer Genome Atlas (TCGA) [46], binary classification by the University of North Carolina (NCU) [47], ternary classification by the University of Texas M.D. Anderson Cancer Center (MDA) [48], and quinary classification by Lund University (Lund) [49], have been extensively studied. Each molecular subclass presents a unique identity which can serve as a prognostic indicator and a predictor of drug response for individual patients that hold substantial relevance for precision diagnosis.

2. MINIMALLY INVASIVE SURGERY (MIS) FOR UROTHELIAL CANCER

UC is a malignant tumor originating from the transitional epithelium of the urinary tract, exhibiting space-time multifocality. It can occur in the renal pelvis, ureter, bladder, and urethra. UC of the bladder is the most common, accounting for over 90% of overall cases. Approximately 5 – 10% of UCs take place in the renal pelvis or the ureter, uni- or bilaterally, collectively termed UTUC [50,51].

UC is managed primarily through surgical interventions. Technological advances have increasingly favored MIS approaches over traditional open surgeries, thereby achieving similar oncological outcomes while minimizing perioperative morbidity and enhancing the recovery of patients. Herein, we delved into the impact and advancements of MIS for the treatment of UC, focusing on robotic nephroureterectomy, and urinary diversion (UD) techniques following RC.

2.1. Robotic Nephroureterectomy Supplanting Open and Laparoscopic Approach for the Management of UTUC

The choice of surgical approaches for UTUC is primarily dictated by the location of the tumor and the patient's overall condition, and they include RNU, segmental ureterectomy, or for select cases, endoscopic resection. Due to the multifocal nature of UC, RNU is considered to be the standard surgical procedure for localized UTUC. A standard RNU involves the removal of the affected kidney, and the entire ureter, and excision of the ipsilateral bladder cuff. Given a high rate of

ureteral stump recurrence at 33 – 75% [50,51], complete excision of the distal ureter down to the intramural ureter and bladder cuff is paramount. Consensus is still lacking about the optimal technique for bladder cuff excision. Matin and Gill retrospectively investigated the recurrence and survival of patients who had undergone RNU using two methods of managing the bladder cuff. The bladder cuff was excised transvesically by cystoscopic secured detachment and ligation (CDL) or extravesically using a laparoscopic stapling (LS). Compared to the CDL, LS resulted in a higher positive margin rate ($P = 0.046$). Moreover, freedom from recurrent tumor was also related to the method of bladder cuff excision used ($P = 0.02$) [52]. Li *et al.* also examined the optimal technique for bladder cuff excision. They retrospectively compared the oncologic outcomes following RNU using three methods of bladder cuff excision, that is, intravesical incision, extravesical incision, and transurethral incision. However, the study found that these three techniques yielded comparable oncologic outcomes, with no significant differences observed in recurrence-free survival (RFS) or cancer-specific survival among the three groups [53].

While open RNU (ORNU) remains the gold standard treatment for UTUC, laparoscopic RNU (LRNU) has been proposed as a minimally invasive surgical alternative during the past two decades. LRNU is associated with a lower risk of surgical complications and shorter hospital stays compared to ORNU. However, the oncological safety of LRNU remains controversial. Fairey *et al.* performed a large, multi-institutional analysis involving 1029 patients from ten centers in Canada to investigate the association between surgical approach and outcomes. They found that the surgical approach was not independently associated with overall or disease-specific survival. However, there was a trend toward an independent association between LRNU and poorer RFS [54]. Peyronnet *et al.* conducted a systematic literature review and compared the outcomes of ORNU and LRNU. They found that LRNU might have poorer oncological outcomes compared to ORNU, particularly when the bladder cuff was excised laparoscopically and in patients with locally advanced high-risk UTUC [55].

Since Eun *et al.* performed the first total robotic nephroureterectomy in 2007, robotic-assisted RNU (RRNU) has undergone multiple modifications and gained popularity in recent years [56-58]. Robotic-assisted surgery offers several technical advantages, particularly in facilitating complex dissections and suturing in confined spaces, which are crucial for procedures such as retroperitoneal lymph node dissection and resection of the bladder cuff. In 2015, Aboumohamed *et al.* first reported the oncological efficacy in a large series of 65 UTUC patients who underwent RRNU with bladder cuff excision. RRNU yielded intermediate-term oncologic outcomes comparable to the published data of ORNU or LRNU. Moreover, RRNU provided a streamlined approach to isolating the distal ureter and excising the bladder cuff [59]. Lee *et al.* conducted a retrospective analysis comparing the oncological and perioperative outcomes of ORNU ($n = 161$), LRNU ($n = 138$), or RRNU ($n = 124$). Their results indicated that RRNU and LRNU were associated with shorter hospital stays, longer operating time, and reduced blood loss compared to ORNU (all $P < 0.001$). In addition, rates of intraoperative and early post-operative complications were similar across the groups, and ORNU was non-inferior to RRNU and LRNU in terms of oncological outcomes [60]. Grossmann *et al.* conducted a retrospective, multicenter propensity score-matched analysis involving 2434 UTUC patients. Their results showed that RRNU and LRNU were associated with significantly worse bladder RFS compared to ORNU. However, LRNU and RRNU had shorter hospital stays and fewer major post-operative complications. Importantly, RFS, CSS, and overall survival (OS) were similar among the three groups [61]. The surgical and oncological data of some studies with large sample size regarding approaches and outcomes of RNU are summarized in Table 1. However, the question about the optimal approach to RNU remains unanswered. RRNU may cause less intraoperative blood loss, have shorter hospital stays, and achieve similar oncological outcomes compared to other approaches, but it was associated with higher surgical costs. Future studies of prospective randomized designs and long-term follow-ups of outcomes are warranted to clarify the optimal approach.

2.2. UD after RC

RC plus regional pelvic lymphadenectomy is a standard surgical procedure for treating localized high-risk BC. However, this extensive pelvic surgery comes with significant surgical risks. The complication and mortality rates associated with open RC (ORC) are typically high. The development of minimally invasive surgical techniques has expanded treatment options for BC patients. Laparoscopic RC (LRC) has emerged as a minimally invasive alternative to ORC, offering advantages such as decreased blood loss, shorter hospital stays, and quicker recovery [67]. In recent years, robot-assisted RC (RARC) has been introduced and is designed to further reduce major complications. Leow *et al.* demonstrated, in the largest comparative cohort study involving 36,773 patients, that RARC was associated with a lower risk of minor complications compared to ORC [68]. However, randomized trial has not definitively shown differences in oncological outcomes between patients treated with ORC and those receiving RARC [69,70].

RC typically requires subsequent UD. The choice of diversion, continent or incontinent, depends largely on

Table 1. Summarization of large-scale studies regarding approaches and outcomes of radical nephroureterectomy

Study ID	Study design	Number of patients, *n*				Follow-up time, months	Surgical outcomes	Oncological outcomes
		RRNU	LRNU	ORNU	Total			
Rodriguez *et al*., 2017 [62]	Nation-wide database	2098	4104	3199	9401	N.D.	RRNU was associated with a greater likelihood of LND performance and lower PSM rates	Surgical approach did not independently affect OS.
Lee *et al*., 2019 [60]	Retrospective, single-center	124	137	161	422	RRNU versus LRNU versus ORNU, 23.7 versus 38.1 versus 41.7 (Mean)	RRNU and LRNU yielded less intraoperative blood loss, shorter hospital stays, and less analgesic usage	The surgical approach did not independently affect OS, CSS, and PFS.
Kenigsberg *et al*., 2021 [63]	Nation-wide database	1129	1502	-	2631	RRNU versus LRNU, 33 versus 35 (Mean)	LRNU was more likely to undergo conversion to an open procedure, had longer hospital stays	RRNU had a better OS.
Li *et al*., 2021 [64]	Retrospective, 15 centers	141	LRNU 458, HALNU 741	-	1340	N.D.	HALNU was significantly associated with longer hospital stay and a higher risk of major complications	HALNU had the worst OS and CSS.
Bae *et al*., 2022 [65]	Retrospective, single-center	119	185	61	365	RNU versus LNU versus ONU, 22 versus 29.92 versus 32.4 (Mean)	Operation time, blood loss, length of hospital stays, and complication rates were not different among the three groups	The surgical approach did not independently affect OS, CSS, and PFS.
Grossmann *et al*., 2023 [61]	Retrospective, multicenter	473	865	1096	2434	32 (overall median)	LRNU and RRNU had shorter hospital stay and fewer major post-operative complications	RRNU and LRNU were associated with significantly worse BRFS. Moreover, OS, CSS, and RFS were similar. among the three groups
Huang *et al*., 2023 [66]	Retrospective, single-center	87	144	-	231	RNU versus LNU, 20 versus 29 (Median)	RANU had a lower intraoperative blood loss and shorter post-operative hospital stay	OS, CSS, and BRFS were similar between the two groups

RNU: Radical nephroureterectomy; ORNU: Open radical nephroureterectomy; LRNU: Laparoscopic radical nephroureterectomy; HALNU: Hand-assisted laparoscopic nephroureterectomy; RRNU: Robotic radical nephroureterectomy; OS: Overall survival; CSS: Cancer-specific survival; RFS: Recurrence-free survival; BRFS: Bladder recurrence-free survival; LND: Lymph node dissection; PSM: Positive surgical margin; N.D.: Not determined.

patient factors and surgeon expertise. Orthotopic neobladders effectively preserve body image by maintaining a more natural urinary function and, thus, represent an optimal choice for many patients. Alternatively, continent cutaneous diversions offer a viable option, allowing urine to be stored in a reservoir created from a section of the intestine and drained through a catheterizable stoma [71]. In contrast, ileal conduits, while being the simplest, least risky, and most common UD, involve redirecting urine through a segment of the intestine to an opening in the abdominal wall, where it is collected in an external pouch [72]. Historically, LRC with extracorporeal UD (ECUD) has been the dominant method due to its surgical feasibility. In recent years, RARC has gained traction. When combined with intracorporeal UD (ICUD), this approach has seen increasing adoption. Initially, in 2005, ICUD was performed in only 9% of RARC cases. However, according to the update from the International Robotic Cystectomy Consortium, the adoption of ICUD has dramatically increased, reaching 97% of cases by 2015 among their groups [73]. The advantages of ICUD include smaller incisions, reduced post-operative pain, minimized bowel exposure, and a decreased risk of fluid imbalance. A recent randomized controlled trial has confirmed that RARC in combination with ICUD is safe and feasible, demonstrating that the perioperative and post-operative complication rates, as well as oncological outcomes of the procedure, were comparable to those observed with ORC [74].

It is important to note the significant learning curve associated with RARC plus ICUD, given the complexity of this procedure. Collins *et al.* demonstrated that mentor surgeons could have significant improvements in operative time and complication rates among 47 patients. They also emphasized that the learning curve for ICUD could be shortened by collaborating closely with a surgeon who has already mastered the technique [75]. Cassim *et al.* reported that previous high-volume experience in performing robot-assisted radical prostatectomy reduced the learning curve for performing RARC [76]. Achermann *et al.* suggested that

technically challenging cases should be undertaken after gaining experience with at least 40 RARC with ICUD, given that operation time, blood loss, and minor complications decrease with increasing surgical experience [77]. According to a 10-year analysis of intracorporeal robotic Padua ileal bladder by Tuderti *et al.*, patients at the beginning of the learning curve experienced significantly longer hospitalizations, more post-operative complications, and lower Trifecta rates. The learning curve was identified as an independent predictor of urinary continence recovery [78]. In short, mentor surgeons should make a dedicated effort to perform ICUD, as this will help overcome the learning curve. Initial concerns about proficiency should not discourage its adoption [79].

3. EMERGING TREATMENTS OF ADVANCED UC (aAU)

Despite recent advances, the 5-year survival rate of advanced-stage urothelial carcinoma (aUC) hovers around 10% [80]. Therefore, aUC is not considered curable by available therapeutic options. Since the 1980s, platinum-based chemotherapy has been the standard first-line option for patients with advanced-stage UC (inoperable or metastatic) [81]. This paradigm has remained unchanged even after the introduction of immune checkpoint inhibitors (ICIs) in recent years as a part of the treatment regimen for metastatic UC (mUC).

Initial results from the phase III JAVELIN Bladder 100 trial (NCT02603432) showed that avelumab first-line maintenance plus best supportive care (BSC) significantly prolonged OS and progression-free survival (PFS) versus BSC alone in patients with aUC who were progression-free after 1L platinum-based chemotherapy [82]. At present, several studies on immunotherapy in combination with maintenance therapy are currently underway. MAIN-CAV trial (NCT05092958) is the only phase 3 trial with a primary endpoint of OS study in this field and the results are very promising. With regard to CheckMate 901 (NCT03036098) [83], a phase 3, multinational, and open-label trial, researchers revealed that combination therapy with nivolumab plus gemcitabine-cisplatin resulted in significantly better outcomes in patients with previously untreated aUC than gemcitabine-cisplatin alone. The final analysis showed that the median OS was 21.7 months in the nivolumab-combination group and 18.9 months in the gemcitabine-cisplatin group. Overall, survival was 70.2% and 62.7%, respectively, at 12 months and 46.9% and 40.7%, respectively, at 24 months.

The treatment landscape for aUC has been transformed by the advent of ICIs, targeted therapies, and, more recently, antibody-drug conjugates (ADCs), which have significantly improved the management of aUC. The initial major change was the introduction of first-line ICIs for patients deemed ineligible for platinum-based therapy [84-86]. As a result of these advances, ICIs have been adopted as second- or third-line therapy for patients with disease progression after platinum-based chemotherapy. For special patients with tumors harboring FGFR alterations, molecular characterization of UC led to the approval of erdafitinib (Balversa®) [87]. More recently, another important milestone was the approval of avelumab as a switch maintenance therapy after first-line chemotherapy, that is not included in the first-line regimen [88].

Finally, the combination of the ADC enfortumab vedotin (EV) with pembrolizumab received fast-track FDA approval as a first-line therapy for patients, regardless of patient characteristics, such as platinum eligibility or programmed death ligand 1 (PD-L1) expression status, which were previously used to guide treatment decisions [89]. Two ADCs have already received regulatory approval for use in patients with aUC, while several others are currently under investigation.

3.1. Anti-nectin-4 ADCs

3.1.1. EV monotherapy and combinations

EV is an ADC targeting nectin-4, a transmembrane protein which is highly expressed in UCs [90]. It was initially granted accelerated FDA approval in 2019 based on findings from the EV-201 trial in cohort 1. An objective response rate (ORR) of 44% (with a complete response [CR] rate of 12%) and median duration of response (mDOR) of 7.6 months were achieved in the cohort, which included 125 patients (pts) with aUC who experienced disease progression or recurrence following a platinum-containing regimen and an ICI [91]. At that time, the standard care of third-line treatment for aUC patients was single-agent chemotherapy, which historically yielded poor results (typically a median PFS [mPFS] <6 ms). EV was rapidly put into clinical practice and granted regular approval. Based on data from a multi-centered, single-arm, phase 2 trial, and EV-201 trial (NCT03219333) [92], its indications were expanded to include patients not eligible for cisplatin-containing chemotherapy and those who had previously received first-line ICI monotherapy. The relevant pre-clinical studies have been completed and shown encouraging results. O'Donnell *et al.* reported the results of Cohort K of EV-103 trail (NCT03288545), leading to accelerated approval of EV and pembrolizumab for cisplatin-ineligible patients. The trail tested this promising combination as first-line therapy in 45 platinum-ineligible patients and revealed a confirmed ORR of 73%, with a CR of 15% [93]. EV + Pembro showed a high cORR with durable responses as 1L treatment in cisplatin-ineligible patients with la/mUC. Adverse effects were more common in the combination arm, with approximately half of

all patients developing any-grade skin rash and/or peripheral neuropathy [94]. Long-term follow-up of the EV-103 dose-escalation cohort and cohort A revealed no new safety concerns after nearly 4 years of follow-up with this combination of EV + pembro. In the same update, the ORR was 73.3% and the disease control rate was 84.4%. The mDOR was 22.1 months and the median OS was 26.1 months [95]. Data from these cohorts provided the rationale for further evaluation of this EV + pembro therapy in Cohort K, a randomized cohort. In Cohort K, patients with aUC who were ineligible for cisplatin were randomized at a 1:1 ratio to receive EV + pembro or EV monotherapy.

The latest update to this cohort indicated that, at the time of analysis, the confirmed ORR was 64.5% and the median DOR was not reached. Importantly, 53% of confirmed ORRs occurred in patients with liver metastases [96,97]. Based on data from the EV-103 trail, including the dose-escalation cohort and cohorts A and K, the FDA granted accelerated approval to EV plus pembro as a first-line treatment for cisplatin-ineligible patients with aUC [98]. The phase 3, open-label, randomized EV-302 trial (NCT04223856) compared the first-line treatment with gemcitabine plus cisplatin or carboplatin with the first-line treatment with EV plus pembro in both cisplatin-eligible and cisplatin-ineligible patients with aUC. The results were positive. Treatment with EV + Pembro led to a clinically relevant benefit over chemotherapy in terms of PFS and OS, the two primary end points, as well as a higher percentage of patients with tumor responses. Tumor responses were observed in two-thirds (67.7%) of the patients in the EV + pembrolizumab group. After 1 year, 50.7% of the patients in the + pembro group were still alive without radiographic progression, compared to 21.6% in the chemotherapy group. The median OS was 31.5 months in the EV + pembro group, against 16.1 months in the chemotherapy group. The beneficial effect of EV and pembrolizumab was consistently observed across several relevant subgroups. Common grade ≥3 treatment-related adverse events (TRAEs) were observed in 55.9% of patients, including maculopapular rash (7.7%), hyperglycemia (5.0%), neutropenia (4.8%), and peripheral sensory neuropathy and diarrhea (both 3.6%) (Table 2) [89]. These findings provided evidence that treatment decisions could be made independent of patient characteristics, such as cisplatin eligibility or PD-L1 expression status, factors on which current treatment decisions are based. Before EV-103 and EV302 trails, no other regimens had conferred such a high ORR; therefore, a new benchmark was introduced. A multi-cohort study investigating doublet and triplet regimens containing EV plus combinations with other anticancer therapies (pembro and/or chemotherapy) or EV as monotherapy for the treatment of aUC across a range of clinical settings is currently underway.

Another group of investigators is conducting the MORPHEUS-UC trial (NCT03869190). This phase Ib/II trial evaluates atezolizumab plus magrolimab, niraparib, or tocilizumab in platinum-refractory locally-advanced or mUC. The project consists of two stages. Stage 1 involved 130 – 305 platinum-treated aUC patients randomized to receive either atezolizumab or monotherapy (control arm) or one of several trial arms: atezolizumab plus either EV, niraparib, magrolimab, isatuximab, linagliptin, or tocilizumab. The primary endpoint is ORR. Safety will be monitored for potential overlapping toxicity. In stage 2, it will expand two of the treatment arms, including atezolizumab plus EV or linagliptin, unless either of the combination is shown to be inactive in the phase 1 trial [99].

3.2. Anti-TROP-2 ADCs

3.2.1. Sacituzumab govitecan (SG) monotherapy

SG, another ADC consisting of an anti-TROP-2-directed ADC containing cytotoxic SN-38, the active metabolite of irinotecan. SG was fast-track approved by the US Food and Drug Administration, based on cohort 1 of the TROPHY-U-01 study (NCT03547973), for the treatment of mUC (locally advanced or metastatic), which was previously treated with platinum-based chemotherapy and an ICI. The trial was a single-arm, multicohort, open-label, and phase II registrational study, which enrolled 113 patients with a UC previously received a platinum-based regimen and either an anti-PD-1 or anti-PD-L1 antibody, and evaluated the efficacy and safety of this agent [100,101]. The initial ORR was 27% with CRs in 5.4% of patients; the median DOR was 7.2 months with a longer follow-up; and the ORR remained high (28%), including responses in patients with heavily pre-treated aUC. Mutations in the UGT1A1 gene are associated with increased adverse events with irinotecan-based therapies. In patients who had previously received EV and those with disease progression on prior adjuvant or neoadjuvant platinum-based therapy, the randomized, open-label, and multi-centered Phase III study TROPiCs-04 (NCT04527991) [102] enrolled patients with metastatic or locally-advanced unresectable UC who had suffered from disease progression after platinum-based chemotherapy and an ICI. Patients received either SG or single-agent chemotherapy chosen by their physician, with a primary end-point of OS. Routine approval for this indication required validation of clinical benefits. In cohort 3 of the TROPHY-U-01 trial (NCT03547973), 61 patients with platinum-refractory aUC who had not received an aUC (ICI) were treated with SG plus pembrolizumab. Interim data from this study indicated an ORR of 34%, a median DOR, that was not reached at the time of analysis, and a 6-month PFS rate of 47% (Table 2). Of note, this cohort included patients with rapid disease progression after neoadjuvant or

Table 2. Selected trails testing ADC-ICI combination in advanced-stage urothelial carcinoma

Trail	Intervention	Outcomes	Adverse events
EV-302 [89] (N=442)	EV plus pembro	ORR 67.7%; mDOR NR (20.2 – NR); mPFS 12.5 months; mOS 31.5 months	Common grade ≥3 TRAEs included maculopapular rash (7.7%); hyperglycemia (5.0%); neutropenia (4.8%); peripheral sensory neuropathy and diarrhea (both 3.6%)
TROPHY-U-01 cohort 3 [102] (N=41)	SG plus pembr o	ORR 41%; mDOR 11.1 months	Grade ≥3 TRAEs in 59% of patients
RC48-C014 [111] (N=41)	DV plus toripalimab	ORRs 73.9% (as first-line therapy) and 71.8% (as later-line therapy)	Common grade ≥3 TRAEs included increase in serum γ-glutamyl transferase levels (12.2%), increase in serum ALT/AST levels (7.3%), and asthenia (7.3%)
DS8201-A-U105 [112] (N=34)	T-DXd (DS-8201) plus nivo	ORR 36.7%; mDOR 13.1 months; mPFS 6.9 months; mOS 11.0 months (data reported only from patients with HER2 IHC scores ≥2+)	Common any-grade TRAEs included nausea (73.5%), fatigue (52.9%), and vomiting (44.1%)

EV: Enfortumab vedotin; pembrolizumab, pembro (anti-PD-1 antibody); SG: Sacituzumab govitecan; DV: Disitamab vedotin; toripalimab (anti-PD-1 antibody); Trastuzumab deruxtecan, T-DXd (DS-8201); nivolumab, nivo (anti-PD-L1 antibody); TRAE: Treatment-related adverse event; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; mDOR: median duration of response; mOS: Median overall survival; mPFS: median progression-free survival; ORR: Objective response rate.

platinum-based adjuvant chemotherapy, with a median time from the last dose of chemotherapy to trial screening lasting for 1.6 months. Additional cohorts of TROPHY-U-01 trial are still under investigation. SG after first-line ICIs therapy alone is being evaluated in cohort 2, and SG plus cisplatin with or without induction therapy with avelumab or the anti-PD-1 antibody zimberelimab, is being studied in cohorts 4 and 5. Switching to maintenance therapy with avelumab or zimberelimab was performed.

3.3. Anti-HER2 ADCs

3.3.1. Trastuzumab deruxtecan (T-DXd, DS8201); disitamab vedotin (DV, vedecitumab, RC-48)

Somatic mutations of *ERBB2* and *ERBB3* (which encode HER2 and HER3, respectively) are found in a wide range of cancers. Genomic alterations in *ERBB2* have been described in UC patients, and multiple trials have assessed the efficacy of anti-HER2 agents in aUC [103]. Overall, *ERBB2* alterations are found in 19% of MIBCs and aUCs, with driver mutations in approximately 10% and amplifications in about 9% [104]. Strategies targeting HER2 with trastuzumab and/or tyrosine-kinase inhibitors (afatinib, neratinib, and lapatinib) have failed to substantially improve outcomes in those with aUC [105-107].

Trastuzumab deruxtecan (T-DXd) and DV (vedecitumab, RC-48) are both anti-HER2 ADCs that consist of an anti-HER2 monoclonal antibody and an MMAE payload. Compared with T-DXd, DV targets HER2 through the humanized monoclonal antibody hertuzumab and has a higher affinity for HER2, which has a greater antibody-dependent cell-mediated cytotoxicity [108]. Unlike many other approved HER2-directed therapies, these ADCs can effectively target tumor cells with low levels of HER2 expression. The cytotoxic payload may also be cytotoxic to neighboring tumor cells through a bystander effect.

The phase II RC48-C011 trial (NCT04073602) evaluated DV in 19 patients with HER2-negative or HER2-low (defined as IHC score 0 or 1+, respectively) locally-advanced or metastatic urothelial cancer. The overall response rate (ORR) was 26% and an additional 68% of patients achieved a stable disease state [109]. In a pooled analysis of data from 107 heavily pretreated patients with HER2-positive (IHC score 2+ or 3+) aUC who received the same agent, the ORR was 50.6% [110]. Preliminary results from a phase Ib/II trial testing DV plus toripalimab (an anti-PD-L1 antibody) in 41 patients with aUC (59% with HER2 IHC scores 2+ or 3+) included an ORR of 75%, increasing to 100% for patients with HER2 IHC score 2+/3+ and PD-L1-positive disease [111]. The most common TRAEs included an increase in serum ALT/AST levels (65.9%), peripheral sensory neuropathy (58.5%), asthenia and appetite decrease (both 56.1%), and hypertriglyceridemia (48.8%). Grade ≥3 TRAEs included increased serum γ-glutamyl transferase levels (12.2%), elevated serum ALT/AST levels and esthenia (both 7.3%), and hypertriglyceridemia and neutropenia (both 4.9%) [111]. In the first-line setting, RC48-C016 study I (NCT05302284), a phase 3, open-label, multicenter, randomized, and controlled study comparing DV plus toripalimab and monotherapy in previously untreated patients with HER2-expressing aUC is ongoing [111]. DS8201-A-U105 (NCT03523572), a phase 1b, multicenter, two-part, and open-label study testing T-DXd in combination with nivolumab showed an ORR of 37% and a median DOR of 13 months in patients with HER2-positive aUC previously on platinum-based therapy [112]. TRAEs were observed in all patients, with grade ≥3 events in 73.5% (44.1% related to T-DXd and 26.5% related to nivolumab). TRAEs leading to drug discontinuation occurred in 32.4% of the patients (17.6% related to T-DXd; 23.5% related to nivolumab). The most common any-grade TEAEs were nausea (73.5%), fatigue (52.9%), and vomiting (44.1%). Drug-related interstitial lung disease/pneumonitis occurred in 23.5% of total patients (Table 2) [112].

3.4. Other ADCs

BT8009 is a second-generation bicycle toxin conjugate targeting nectin-4, a well-validated tumor antigen, and delivers toxin payloads MMAE to tumors. It distributes more rapidly into tissues, penetrates broadly into tumors, and thus delivers drugs faster into tumors and has limited systemic exposure time (approximately 1 h) and renal clearance (liver sparing 140) for benefits [113].

Investigators reported results of the BT8009-100 trial (NCT04561362), an ongoing phase I/II, multicenter, and open-label dose-escalation study of BT8009, including an ORR of 50% and a 16-week clinical benefit rate of 75% in eight evaluable patients with an aUC [114].

4. CONCLUSION

The management of UC has undergone significant transformations rooted in technological advancements, which have positively changed the landscape of UC diagnosis and treatment. With regard to the diagnostic process, novel techniques that are precise, convenient, and non-invasive have emerged and are being incrementally integrated into clinical use. AI, in particular, has demonstrated promising potential for precise diagnosis due to its efficiency in handling high-resolution data. As for surgical intervention, MIS such as LRNU and RRNU has become the preferred techniques, and ICUD, a method of UD, has also seen growing adoption in recent years. For addressing aUC, chemotherapy remains a traditional treatment choice, yet ICIs and targeted therapies have also exhibited impressive results. ADCs, which combine a monoclonal antibody chemically connected to a drug, also showed promising results, with two having been currently approved for use due to their clinical benefits. While the application of these advancements in both diagnostics and treatments has improved patient outcomes, significant challenges, including the recurrent nature of the disease and associated medical complications, remain. Therefore, it is crucial that the medical communities continue to endeavor to achieve more in the diagnosis and treatment of the condition, thereby enhancing treatment efficacy and ultimately, survival rates. The emerging new diagnostic techniques, improved surgical techniques, more efficacious drugs, and continued clinical researches are all giving rise to a promising prospect in the management of UC.

ACKNOWLEDGMENTS

None.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

DATA AVAILABILITY

Not applicable.

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