Review Article on Management of Advanced Genitourinary Malignancies

Characteristics of upper urinary tract urothelial carcinoma in the context of bladder cancer: a narrative review

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Abstract: Urothelial carcinomas (UC) arise from the urothelium that covers the proximal urethra, urinary bladder, and the upper urinary tract. In daily routine and clinical trials UC originating from different locations are often treated and investigated in the same manner. However, differences between the two locations seem to be apparent and may question in handling them as a single oncologic entity. In this review we discuss similarities and differences between bladder and upper urinary tract UC and consider their potential impact on treatment strategies. Despite similarities of UC in the bladder (BC) and the upper urinary tract (UTUC), clinicopathologic and molecular differences may question to generally assemble both as a single tumor entity. Treatment standards for UTUC are often adopted from BC. However, a specific investigation in the former may still be meaningful as shown by the example of adjuvant cisplatin based chemotherapy. In conclusion, future investigations should prioritize the understanding of the tumor biology of both BC and UTUC. This may reveal which UTUC can be treated according to treatment standards of BC and in which cases, a separate approach may be more appropriate.

Keywords: Urothelial carcinomas (UC); bladder cancer; upper urinary tract

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Introduction

Urothelial carcinomas (UC) are the 7th most common cancers and can be located anywhere where a body surface covered with urothelium is present. In the clinical practice UC are historically divided in three groups: UC of the bladder (BC), upper urinary tract UC (UTUC) and urethral carcinoma. BC accounts for 90–95% of UC (1,2). UTUC, defined as a malignancy arising from urothelial cells in the ureter and/or pyelocaliceal cavities, accounts for 5–10% of all UC. Primary urethral carcinoma is rare and accounts for <1% of all genitourinary malignancies (3).

UC of the bladder and the upper urinary tract share histomorphological similarities. However, differences between both may still be relevant. Embryologically, the urinary bladder and the upper urinary tract arise from two different germ cell layers. Both are exposed to carcinogens and toxins excreted in urine. However due to their function, their exposure is different. The bladder stores the urine and its urothel is subsequently exposed for a longer period, while the upper tract transports the urine and is only exposed for a short term (4,5). Differences can also be observed at

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initial staging. While 75–85% of patients present with non-invasive BC, only a third of patients with UTUC have non-invasive disease (6).

Based on similarities between both, current diagnostic and therapeutic strategies overlap. Moreover, in clinical practice metastatic UC are considered and treated as a single oncologic entity, regardless of the primary tumor location. Also in clinical trial settings both are often included in similar or even in the same trial. This may be in contrast to findings from molecular investigations that revealed similarities but also differences between BC and UTUC.

In this review, we aim to perform a comparison between BC and UTUC with regard to clinical, pathological, molecular and therapeutic characteristics.

We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/tau-20-1472).

Methods

The authors have acquired the evidence for the narrative review in articles indexed online in the MEDLINE literature database through PubMed (http://ncbi.nlm.nih.gov/pubmed) between April 2020 and October 2020.

Clinical characteristics (*Table 1*)

Gender

Men are three times more likely to develop BC than women (2) and are more frequently diagnosed with non-muscle invasive BC, whereas women present more advanced tumor stages and worse prognosis when compared to their counterparts (7-12). The occurrence of metastatic disease, however, is similar between genders (7-13).

In contrast, UTUC is only 1.5–2 times more common in men than women (14,15). In some Balkan regions females more often present UTUC, when compared to males. The underlying pathophysiologic mechanism has not fully been unveiled yet (see section: Geographical distribution and associated risk factors) (16,17).

Age

BC is generally a disease of the elderly, with a median age at approximately 70 years at diagnosis (18,19). In line with BC, the incidence of UTUC increases with patient age with a peak incidence at 70–90 years. Not surprisingly, increasing age at diagnosis has been associated with inferior outcomes (20).

Geographical distribution and associated risk factors

The incidence of urothelial BC is enriched in developed countries. In contrast, the incidence of squamous cell carcinoma of the urinary bladder is high in some African and Asian countries because of endemic Schistosomiasis (21). Tobacco smoking significantly increases the risk of both BC and UTUC and is responsible for half of the BC cases in some populations (18,22,23).

The prevalence of UTUC is regionally enriched in Balkan and Asian regions such as Taiwan (24). The underlying rationale for this enrichment has not fully been unravelled. An association of UTUC and black foot disease or a high content of arsenic in the drinking water is assumed. Since the 1950, also in Balkan regions a high incidence of UTUC has been described (in some areas 60–100 times higher than the rest of the world) (25). Both, this so called Balkan endemic nephropathy as well as the Chinese herbs nephropathy (CHN), are chronic tubulointerstitial renal diseases that are associated with an increased risk of UTUC (26). Both have been linked to an exposure to aristolochic acid, which has nephrotoxic and carcinogenic effects. These above mentioned parameters are considered to cause an increased incidence of UTUC in females (see section: Gender).

Pathological differences (*Table 2*)

Urothelium covers the urinary tract from the intrarenal collecting system, ureter, bladder and urethra. Basal stem cells of the urothelium proliferate and differentiate to luminal and finally umbrella cells. During this maturation, UC can arise from each cell phenotype. Consequently, UC presents a wide range of phenotypes and different histomorphologic characteristics (27). The World Health Organisation Classification of Tumours of the Urinary System and Male Genital Organs of 2016 classified no more than 13 different histological variants (28). Some histological variants are associated with an unfavourable prognosis (29). However, the current clinical management is only minimally affected by these different morphological patterns. Although mainly characterized in BC, the histological variants are also used to describe UTUC.

Most BC present a pure or conventional urothelial

Table 1 Clinical characteristics

	BC	UTUC
Epidemiology		
Peak incidence (y)	80	80
Percentage of all UC	90–95%	5–10%
Men:women ratio	3–4:1	1.5–2:1
Geographical enrichment	Developed countries; African and Asian countries because of endemic Schistosomiasis (squamous cell carcinoma of the bladder)	Balkan countries and the Asian region Taiwan
Risk factors		
Tobacco smoking	Yes	Yes
Aromatic amines	Yes	Yes
Pelvic radiotherapy	Yes	No
Bladder schistosomiasis	Yes	No
Chronic urothelial infection	Yes	Possible
Aristolochic acid	Possible	Yes
Genetic factors	Only scarcely explored	Lynch syndrome
Arsenic in drinking water	Possible	Possible
Others	Thiazolidinediones, metabolic disorders, chlorinated drinking water	Alcohol consumption
TNM classification		
T-stadium	Subclassification for T2, T3 and T4	No subclassification
N-stadium	Dependent of number and anatomic location: N1, N2, N3	Dependent of lymph node dimension: N1, N2
M-stadium	M1a: non-regional lymph nodes M1b: distant metastasis	No subclassification
Diagnostic work-up		
Cystoscopy and urinary cytology	Yes	Yes
Transurethral resection of invasive bladder tumours (TURBT)	Yes	if suspected BC
Diagnostic ureteroscopy with biopsy and/or selective cytology	If suspected UTUC	Yes
Staging with lung- and abdominal computed tomography (or Magnetic resonance urography)	Yes	Yes

BC, bladder urothelial carcinomas; UTUC, upper urinary tract urothelial carcinomas; UC, urothelial carcinomas.

histology and a third of the urothelial BC show a concomitant variant histology (28). They are often associated with high grade disease and locally advanced stages (30,31). In contrast, in UTUC only a quarter of the carcinomas present variant histology (32,33). In line to BC, they seem to represent more aggressive biological features and are independent risk factors for unfavourable prognosis (34).

Finally, there are minimal differences in the TNM classification between BC and UTUC (35). In BC, infiltration into the detrusor muscle (pT2a/b), the

Table 2 Pathological and molecular features

Feature	BC	UTUC
Histology		
Classification	According to the World Health Organisation and Male Genital Organs of 2016	Classification of Tumours of the Urinary System
Conventional:variant	90–70%:10–30%	75%:25%
Variant histology associated with aggressive biological features and independent risk factors for unfavourable prognosis	Yes	Yes
Molecular features		
Mutations in NMIBC	FGFR3, Chromosome 9 loss of heterozygosity, PIK3CA, Ras gene mutations	
MIBC	TP53 (more frequently mutated in BC than in UTUC), RB, PTEN, ERCC2	
High-grade UTUC		FGFR3 (more frequently mutated in UTUC than BC), TP53, HRAS, KMT2D, CDKN2B, ARID1A
Classifications	Baylor, UNC, MDA, TCGAC, CIT-Curie and Lund	Single study subtype classification proposed. Relevant heterogeneity and no association with molecular subtypes of BC
Consensus classification	In 2020, six classes: luminal papillary (LumP, 24%), luminal nonspecified (LumNS, 8%), luminal unstable (LumU, 15%), stroma-rich (15%), basal/squamous (Ba/Sq, 35%), and neuroendocrine-like (NE-like, 3%)	No consensus classification

BC, bladder urothelial carcinomas; UTUC, upper urinary tract urothelial carcinomas; MIBC, muscle-invasive bladder cancer; NMIBC, non-muscle-invasive bladder cancer.

perivesical fat (pT3a/b) and adjacent organs (pT4a/b) are further classified and acknowledged in different primary tumor stages. Number and location of lymph node metastases is taken into account to quantify three different stages in case of involvement. Finally, metastatic BC is differentiated into non-regional lymph nodes and other metastasis. Differences in the TNM staging of UTUC are that likely due to the thinner smooth muscle layer, a further subclassification into pT2a and b is not performed. Also infiltration beyond the muscle layer and adjacent organs are not further distinguished. Number as well as size of lymph node metastases are considered and classified into two pN stages in case of lymph node involvement. Finally, in contrast to BC, no further subclassification of metastatic UTUC is performed.

Molecular landscape of advanced UC (*Table 2*)

Large-scale tumor profiling of BC and UTUC dramatically improved our understanding of their molecular landscape. Moreover, these investigations suggested clinical implications on diagnostic and therapeutic strategies. UC of the bladder is 10 to 20 times more frequent than in the upper urinary tract and for this reason the emerging evidence on biology of UC using high-throughput molecular profiling is mainly due to studies on BC. High-throughput sequencing technologies and publicly accessible large-scale molecular databases [e.g., The Cancer Genome Atlas (TCGA), International Cancer Genomics Consortium (ICGC), Pan-Cancer Analysis of Whole Genomes (PCAWG)] and dataset generated from single centers

offered an extraordinary opportunity in understanding cancer biology. Breast and lung cancer have been the first malignancies that were classified into clusters based on molecular characteristics (36). These concepts contributed to the understanding of tumor pathogenesis. Moreover, the discovery of these so called molecular subtypes contributed to the discovery of prognostic biomarkers and the possibility to predict treatment response. Finally, they allowed even the development of tumor-specific targeted therapies (37).

Bladder

Investigations on phenotypic variants and the prevalence of occult mutational signatures revealed the remarkable heterogeneity of BC more than a decade ago. Based on biological characteristics dependent on molecular pathways and clinical outcomes suggested a two pathway model for tumor pathogenesis: papillary tumors, in the clinical practice frequently non-muscle-invasive bladder cancer (NMIBC) and flat/non-papillary tumors, similar to muscle-invasive tumors (38,39). Approximately three quarters of BC are non-muscle invasive and most of them are characterized by a papillary histology with near-diploid karyotype and few genomic rearrangements. Frequent mutations associated with NMIBC are FGFR3 (in up to 80% of pTa tumors), Chromosome 9 loss of heterozygosity (LOH) (32–48%), PIK3CA (25%) and Ras gene mutations (*HRAS*, *KRAS2*, *NRAS*). TP53 alterations seem to play a major role in high-grade tumors and MIBC, and have been associated with progression of NMIBC in MIBC. However, progression from NMIBC to MIBC also occurs in genetically stable BC, likely due to CDKN2A loss. Multitudes of other genes have been described in the pathogenesis of NMIBC: *TERT*, *CCND1*, *CCND3*, *FGFR1*, *ARID1A*, *ERBB2*, etc. (40-46).

In the two-pathway model, invasive urothelial cancer seemed to arise through a distinct mechanism than papillary and NMIBC. In MIBC, molecular analysis suggested that flat dysplasia may precede development of UC in situ (CIS) and finally invasive UC (47).

TP53 and 9p and 9q LOH play a crucial role in the early pathogenesis of CIS (48). TP53 is commonly mutated in CIS (72%) and is inactivated in 76% of MIBC. Chromosome 9 deletions are frequently present in CIS and MIBC (40,48).

This two-pathway approach was a first step in understanding the evolution of UC, but did not lead to any concrete consequence in the clinical practice. In 2016, Hedegaard *et al.* classified NMIBC into three molecular subtypes (class I, II and III) (49). Class I tumors showed the best prognosis and luminal characteristics whereas class II tumors showed also luminal characteristics but an inferior prognosis and genomic instability (e.g., TP53 loss, ERCC2 mutations). Both classes can also be identified in MIBC (class I - Luminal papillary, class II - Luminal unstable). This may help to refine the two-pathway model and to explain the evolution of bladder cancer. Contrarily, class III tumors presented with a basal like phenotype and did not show similarities to molecular characteristics identified in MIBC (50). The Lund group was the first to attempt a molecular classification system in BC (51). An increase in the size or their dataset revealed a finer grained classification system to five subtypes (52). Finally, five years later, they were also the first that identified the neuroendocrine-like subtype (53).

In 2014, TCGA published their initial analysis of a multiplatform analysis of 131 MIBC (54). They identified two basal and two luminal subtypes. In 2017, after an extension of their cohort to 412 MIBC, they updated their classification system and proposed five molecular subtypes (55).

In 2014, Choi *et al.* (MDA group) proposed, reminiscent of breast cancer molecular subtyping, a subclassification of MIBC in basal, luminal and "p53-like" subtypes (56).

Also in 2014, Damrauer *et al.* (UNC group) proposed a 47-gene set predictor in the effort to identify and predict molecular and clinically subtypes within high-grade UC. They defined two distinct molecular subtypes: luminal and basal-like. A claudin-low subset of tumors was also noted and led the same group in 2016, to propose a third distinct molecular subtype characterized by low expression levels of claudins (57,58).

Although all proposed subtyping classifications share a common concept of subdivision between a basal and luminal tumors, an evident heterogeneity in the further subtypes exists. In tumors with high mutation frequency, like UC, >3,000 samples might be needed to detect a distinct rare subtype with a frequency of <2% (59). Growing cohort numbers imply an increase in detection of further subtypes, like observed for example in the TGCA and Lund classification during the years. Another major limitation is that all proposed classifications are characterized by heterogeneity when considering the studied populations, with either classifications based on MIBC, NMIBC or both together. Furthermore over the time there was growing evidence that microenvironment and non-tumor cells play a major role in the global understanding of UC.

All these aspects are especially relevant if we consider improvement of treatment and focus on personalized oncology

as the main goals. While expanding the cohorts, the need for unified classification was growing and was an urgently needed step: a consensus classification allows the transfer of molecular subtyping into clinical practice and precision oncology, and unifies the terminology for future studies.

In 2020 a consensus molecular classification of MIBC, based on 1750 MIBC transcriptomic profiles from 16 published datasets, has proposed six molecular classes: luminal papillary (LumP, 24%), luminal nonspecified (LumNS, 8%), luminal unstable (LumU, 15%), stroma-rich (15%), basal/squamous (Ba/Sq, 35%), and neuroendocrine-like (NE-like, 3%). The classification was strongly associated with each of the input classification systems (Baylor, UNC, MDA, TCGAC, CIT-Curie and Lund). These classes present different molecular signatures, microenvironment infiltration, histological and clinical characteristics, as well as distinct outcomes (60).

Upper tract urothelial carcinoma (UTUC)

Compared to BC, genetic analysis and high-throughput sequencing of UTUC is much less reported in the literature and few studies with genomic characterization of UTUC have been published.

In 2015, Sfakianos *et al.* (5) analyzed 83 tumor samples from patients with high-grade (n=60) and low-grade (n=23) UTUC treated with radical nephroureterectomy and (n=102) samples from BC in patients without history of UTUC. Cancer-associated genes and somatic mutations were evaluated and a comparison of the molecular profile between BC and UTUC was performed. The most frequent mutated genes in high-grade UTUC were *FGFR3* (35.6% *vs.* 21.6% in BC, P=0.065), *TP53* (25.4% *vs.* 57.8% in BC, P<0.001), *HRAS* (13.6% *vs.* 1.0%; P=0.001), *CDKN2B* (5.3% *vs.* 3.9%; P=0.016), *ARID1A* (27.5% *vs.* 13.6%, P=0.050). The study showed that despite a similar spectrum of cancer-associated genes in BC and UTUC, there is a relevant heterogeneity in the prevalence of the mutations between the two entities (5).

In 2017, Moss *et al.* (61) published a comprehensive genomic analyses of low-grade (n=14) and high grade (n=17) UTUC samples after endoscopic biopsy or surgical resection in 31 patients. The following mutation frequencies were reported *FGFR3* (74.1%; 92% low-grade, 60% high-grade), *KMT2D* (44.4%), *PIK3CA* (25.9%), and *TP53* (22.2%). Interestingly *FGFR3* was mutated in 60% of the invasive UTUC compared to 35.6% reported by Sfakianos *et al.* in 2015 (5). Furthermore, using unsupervised consensus clustering of RNAseq expression data, four molecular subtypes were generated with some similarities to the TCGA clusters for BC. Comparing these results to the TGCA 2014 classification, global mutation rate in BC and UTUC were similar (54,61).

In 2018, Donahu *et al.* analyzed germline mutations in UTUC patients (n=17) with Lynch syndrome and compared the results with a cohort of 82 sporadic UTUC. Interestingly, after a pathological review of the sections, they found no variant histology in their UTUC cohort. In line with the underlying biology of Lynch syndrome, UTUC in these patients are associated with a significant higher mutational burden as well as higher frequency of genomic alterations in *KMT2D*, *CREBBP*, *ARID1A* or in DNA damage response and repair genes. Contrarily, mutations in CIC, *NOTCH1*, *NOTCH3*, *RB1*, and *CDKN1B* genes were only found in the control population (62).

Robinson *et al.* compared in 2019 genomic analysis from patients with high-grade UTUC (n=37), with data from BC tumors from the TCGA cohort. As already observed FGFR3 was less frequently mutated in high-grade BC (13.7%) compared to high-grade UTUC (29.7%). In contrast, no significant difference in the prevalence of mutations between UTUC and BC were reported for *KMT2D*, *ARID1A*, *KDM6A*, *PIK3CA*, *HRAS*, *RXRA*, *KLF5*, *ELF3*, *TP53*, *RB1*, *CDKN1A*, *CDKN2A*. UTUC were consistently luminal-papillary and T-cell depleted, which seems to be related with an unfavorable response to checkpoint inhibitors (63).

Audenet *et al.* performed a genomic analysis in 454 BC (94% high-grade) and 195 UTUC (85% high-grade) patients, and investigated clonal similarities of 29 patients with metachronous UTUC and BC. Overall, *FGFR3* and *HRAS* were more frequently mutated in UTUC (40% *vs.* 26%, 12% *vs.* 4%, respectively; Q <0.001), *TP53*, *RB1*, and *ERBB2* were more frequently mutated in BC (46% *vs.* 26%, 20% *vs.* 3%, 19% *vs.* 8%, respectively; Q <0.001). The mutational burden was significantly higher in UTUC compared with BC, with patients presenting Lynch syndrome associated gene mutation showing high mutational burden. Clonal relatedness was confirmed for all (n=29) patients with bladder recidivism, with a concordance of 86% of somatic mutations in both the initial UTUC and the subsequent BC (64).

Therapies and the role of high-throughput molecular profiling (*Table 3*)

Therapy of BC in 2020

The standard of care for the treatment of NMIBC contains transurethral resection of the bladder tumor (TURBT).

Table 3 Therapies and outcomes

	BC	UTUC
Therapy non-muscle invasive		
Low-grade	TURBT + single post-operative intravesical instillation of chemotherapy	Endoscopic ablation (e.g., by laser ablation); CAVE: absence of hydronephrosis, tumor size <2 cm, solitary disease, absence of variant histology and absence of previous high-grade tumors
High-grade	TURBT + second TURBT (2–6 weeks) and + Instillation Therapy (BCG > Chemotherapy)	See muscle invasive UTUC
Primary CIS	TURBT + Instillation Therapy (BCG > Chemotherapy)	See muscle invasive UTUC
Therapy muscle invasive		
Neoadjuvant chemotherapy	Indicated in T2–T4a, cN0M0 with cisplatin-based combination therapy	To date, no prospective trial has been published on this topic
Neoadjuvant immunotherapy	Investigated in clinical trials, but Phase III data have not been published yet	To date, no prospective trial has been published on this topic
Surgery	Radical cystectomy (RC), pelvic lymphadenectomy and subsequent urinary diversion	Nephroureterectomy with excision of bladder cuff and regional lymphadenectomy and single postoperative intravesical instillation with chemotherapy
Adjuvant therapy	Limited to patients with pT3/4 and/or N+ disease without metastases with cisplatin-based combination therapy	The POUT trial showed that platinum-based chemotherapy significantly improved disease-free survival in locally advanced UTUC
Adjuvant immunotherapy	Investigated in many clinical trials, but data have not been published yet	To date, no prospective trial has been published on this topic
Alternatives	Bladder preserving therapies, like multimodality treatment (MMT) which combines transurethral maximal resection, chemo- and radiotherapy	Segmental ureterectomy with reimplantation of the ureter (provide similar outcomes as RNU, with the advantage of preserving kidney function)
Recurrence and outcomes		
Recurrence and risk factors	NMIBC: local recurrence rate after TURBT: 1-yr recurrence rate 15–61%; 5-yr recurrence rate 31–78%	Bladder recurrence: after RNU for UTUC is 22–47%
	Risk factors: presence of CIS, High-grade features, stage T1 tumor, number of tumors, tumor diameter, prior recurrence rate	Risk factors: advanced age, male gender, ureteral tumor location, laparoscopic surgical technique, endoscopic distal ureteral management, previous bladder cancer, higher tumor stage, concomitant carcinoma in situ (CIS), and lymph node involvement (LVI)
	MIBC: Distant recurrence is seen in up to 50% of patients treated with RC for MIBC	Distant recurrence: after RNU 20–65%
	Risk factors: advanced disease and nodal involvement	Risk factors: Concomitant CIS, LVI, higher tumor stage, multifocality
The 5-year specific survival	pTa/pTis/pT1 >75%	pTa/pTis/pT1 >90%
	pT2/pT3 ~ 50–75%	pT2/pT3: <50%
	pT4 <50%	pT4/M1 <10%
	M1 <10%	

BC, bladder urothelial carcinomas; UTUC, upper urinary tract urothelial carcinomas.

In case of low risk disease, an early postoperative chemotherapy instillation of the bladder reduces risk of recurrence. In high risk disease, a confirmation TURBT is suggested, followed by intravesical instillations with BCG (65,66). The first-line treatment of CIS is not surgical but performed with BCG instillations with a complete response rate in 72–93% patients (67-69). One in two patients with initial complete response is likely to show recurrence with the need of further installation therapies or RC (68,70,71).

The standard of care for the treatment of MIBC contains radical cystectomy, pelvic lymph node dissection and urinary diversion (6,72).

To improve patient outcomes, perioperative chemotherapy has been investigated. Cisplatin based neoadjuvant chemotherapy, which has been used since 1980s, was studied in several RCTs which demonstrated a statistically relevant survival advantage in patients with MIBC prior to surgery. A recent meta-analysis on (n=3,285) patients compared clinical outcomes of MVAC: methotrexate, vinblastine, doxorubicin, and cisplatin *vs.* GC: gemcitabine and cisplatin/carboplatin in the neoadjuvant setting. Cisplatin-based neoadjuvant chemotherapy showed a 16% reduction in overall death risk, compared with locoregional therapy alone and absolute survival benefit of 8% at 5 years (6,73,74).

Neoadjuvant immunotherapy is increasingly being tested in the neoadjuvant setting either in platinum-ineligible patients or as combination therapy. The use of checkpoint inhibitors is already approved as first-line treatment in patients ineligible (unfit) for cisplatin and as second-line immunotherapy for platinum-pre-treated patients with progressing metastatic UC. Based on the results of checkpoint inhibitors in metastatic UC, several clinical trials are investigating the role of novel immunotherapeutic approaches in the preoperative setting. The preliminary results of a Phase II study using the PD-1 inhibitor pembrolizumab in the neoadjuvant setting for MIBC before RC showed promising results with complete pathological remission (pT0) in 42% of patients. programmed death ligand 1 (PD-L1)-expressing or high-Total mutational burden were both predictors of clinical response (75).

The role of adjuvant cisplatin-based chemotherapy in MIBC is limited to patients with pT3/4 and/or LN positive (N+) disease without metastases (cM0). Evidence supporting the use of adjuvant chemotherapy in MIBC is limited and not conclusive (6,76,77). In 2014, a meta-analysis based on 945 patients from nine trials, evaluated outcomes in patients receiving adjuvant chemotherapy after RC. Despite the trials were characterized by relevant methodological flaws and different chemotherapy protocol, this meta-analysis concluded an overall survival [pooled hazard ratio (HR): 0.77; 95% CI, 0.59–0.99; P=0.049] and disease-free survival (HR: 0.66; 95% CI, 0.45–0.91; P=0.014) benefit in patients with MIBC receiving adjuvant cisplatin-based chemotherapy after RC. The impact on DFS in patients with nodal involvement was more evident (76).

Furthermore, a multi-center, phase 3 trial of 284 patients with non-metastatic MIBC randomly assigned either to immediate adjuvant cisplatin-based chemotherapy or deferred chemotherapy at relapse showed significant prolonged progression-free survival for immediate treatment (HR 0.54; 95% CI, 0.4–0.73; P<0.0001), without significant difference in overall survival (78).

To summarize, the role of adjuvant chemotherapy in the treatment of MIBC remains unclear. Based on the current evidence, immediate cisplatin-based adjuvant chemotherapy after cystectomy seems to improve outcomes, especially in non-variant histology and high-risk groups with nodal involvement and extravesical extension.

Adjuvant immunotherapy is investigated in many clinical trials, but data have not been published yet.

UTUC in 2020

According to the EAU Guidelines, low-risk UTUC is defined by: absence of hydronephrosis, tumor size <2 cm, low-grade cytology or URS biopsy, solitary disease, absence of variant histology and absence of previous high-grade tumors (14).

In low-risk UTUC, nephron-sparing treatment, e.g., by laser ablation can be offered (79). Whether a single early postoperative instillation of a chemotherapeutic agent (retrograde through a SJ or DJ) would prevent recurrence has been investigated in only one non-controlled study based on which a final recommendation cannot be made (80). In case of CIS in the upper urinary tract, the instillation of BCG has been investigated (14,81,82). Only scarce evidence exists for the success of this treatment approach and a more recent publication even questions the responsiveness of CIS in the upper urinary tract to BCG (83). However, it is questionable, if one can justify radical surgery for CIS only in the upper urinary tract as treatment in the first-line.

In case of high-risk UTUC radical surgery is recommended. This includes nephroureterectomy with excision of bladder cuff and regional lymphadenectomy. In selected cases with tumors located in the ureter or

patient with solitary kidney or compromised renal function, treatment with kidney-sparing surgery can be offered.

For organ confined tumors located in the ureter, segmental ureterectomy (SU) with reimplantation of the ureter has been shown to provide similar outcomes as RNU, with the advantage of preserving kidney function (14,84). In 2016, a meta-analysis of 11 retrospective studies with 3,963 patients who underwent either SU (n=983; 24.8%) or RNU (n=2,980; 75.2%) reported no significant differences in terms of CSS and OS between both groups, with SU providing a significant decreased risk of postoperative renal function impairment (85). However, these results should be interpreted with caution, because patients undergoing kidney-sparing techniques often present with favorable clinical and oncological characteristics compared to patients undergoing RNU, which can generate selection bias.

Oncological outcomes between open and laparoscopic RNU have been studied in a systematic review of 42 studies in 2019 (86). Among 7,554 patients, 4,925/7,554 (65%) underwent open RNU and 2,629/7,554 (35%) laparoscopic RNU. They concluded that in a subgroup of patients with non-organ confined UTUC (pT3/pT4) as well as in patients with laparoscopic bladder cuff removal, oncological outcomes of laparoscopic RNU tend to be poorer compared to open RNU.

Intravesical recurrence (IVR) after radical surgery for UTUC occurs in 22–47% of the cases (14,87). To prevent intravesical tumor-cell dissemination after manipulation and surgery of advanced UTUC, the effect of a single postoperative intravesical instillation with chemotherapy (mitomycin C, pirarubicin) has been studied in a meta-analysis in 2013 (88). In five trials on 614 patients, with a median follow-up of 12, 55.6, 46 and 45 months (data were incomplete in one trial), IVR was present in 55/268 (20.5%) patients who received postoperative instillation and 127/346 (36.7%) who had no postoperative instillation, with a significant decrease of 41% in the odds of recurrence.

Perioperative systemic treatment in UTUC is not studied to a similar extent as in BC.

Based on the observations and results obtained through neoadjuvant chemotherapy in the treatment of bladder carcinoma, several retrospective studies have investigated the role of neoadjuvant therapy in UTUC. Utilizing preoperative cisplatin-based chemotherapy, pathological downstaging as well as lower recurrence rates and better outcomes have been observed (14,89-92). To date, no prospective trial has been published on this topic.

Similarly adjuvant chemotherapy for UTUC has been investigated based on data adopted from BC. A limitation of cisplatin-based chemotherapy in the adjuvant setting is given by the patient's kidney function, which may be impaired or reduced in patients after RNU. To date only one prospective study has been published on adjuvant systemic chemotherapy for UTUC. In 2020 the results of a multi-center, randomised study of 261 patients with UTUC after RNU staged as either pT2–T4 pN0–N3 M0 or pTany N1–3 M0, were randomly assigned to either surveillance or platinum-based chemotherapy. Chemotherapy conferred a 55% reduction in relative risk of disease recurrence or death. At a median follow-up of 30.3 months, adjuvant chemotherapy significantly improved 3-year DFS (71% in the chemotherapy group *vs.* 46% in the surveillance group). Based on these results, potential similar survival advantages should also be expected in the neoadjuvant therapy, but further prospective studies are needed (93).

Future development, high-throughput molecular profiling and personalized therapies

During the last decade, the first studies on molecular phenotyping were descriptive and aimed to allocate bladder cancer in subgroups that were considered to harbor common molecular and clinical characteristics. The technological advancements in genomic profiling as well as the development of machine learning algorithms and software to process the large amount of data, provided the ability to generate subtyping models and interpret these results. Despite all efforts, the transfer of knowledge into clinical practice is an inevitably long process, made complex by the heterogeneity of the study populations as well as the relative rarity especially of UTUC. This process is still ongoing and only few, but significant, innovations have been made in the treatment of UC.

Choi *et al.*, published in 2014 the first study attempting to investigate the sensitivity of three distinct molecular subtypes (basal, p53-like, luminal) to conventional cisplatin-based neoadjuvant chemotherapy. They observed that "p53-like" MIBCs were consistently resistant to frontline NAC. Basal subtype tumors that responded to NAC were enriched with biomarkers reflective of immune infiltration, and luminal tumors partly responded to NAC but for this subtype pretreatment gene signatures could not be found (56). The same group in 2016 investigated clinical outcomes in 60 patients receiving dose-dense cisplatin-based NAC in addition to Bevacizumab. They allocated (n=38) pre-NAC TURBT specimens using the three molecular

subtype panels previously described. "p53-like" tumors had again poorer outcomes (5-yr OS: 36%) and higher rate of metastasis following NAC compared to basal (5-yr OS: 91%) and luminal tumors (5-yr OS: 73%) (94).

An important limitation for clinical implementations of these results, is that molecular phenotyping is based on relative gene expression. The need to analyse an entire cohort in order to assign a tumor to his subtype limits substantially the use in the clinical practice. To address this issue, in 2017, Seiler *et al.* proposed a single-sample classifier to predict bladder cancer subtype based on transcriptomic analysis of TURBT specimens. They correlated the outcomes after NAC in a large multi-center cohort (n=269) with molecular subtyping of pre-NAC specimens and confirmed the clinical utility of four subtypes: claudin-low (is a EMT and immune infiltrated subgroup of basal tumors with poor outcomes, regardless of NAC), basal (showed most benefit from NAC with dramatically improved outcomes), luminal-infiltrated (appear to have poor prognosis with and without NAC), luminal (had the best prognosis non-treatment dependent, question the utility of NAC) (95).

Chemoresistance to standard cisplatin-based protocols highlighted the need of trials to investigate alternative therapies as well as the need of biomarkers to predict response.

In the IMvigor 210 trial, patients with inoperable locally advanced or metastatic UC whose disease had progressed after platinum-based chemotherapy, were treated with atezolizumab, a monoclonal antibody that binds selectively to PD-L1. Surprisingly the neuronal subtype, which was associated with the worst survival in the TCGA 2017 cohort, had the best overall survival among the five subtypes in the atezolizumab-treated cohort (96,97).

A phase II trial on 270 patients with platinum-based chemotherapy resistant metastatic or unresectable UC showing disease progression, investigated response to the PD-1 human IgG4 monoclonal antibody Nivolumab. The greater response to Nivolumab was in the TGCA III subtype where 30% of the patients had complete or partial responses (98).

The ABACUS trial was not able to show different pathological response among different subtypes based on the Lund classification in patients (n=95) with MIBC receiving two cycles of atezolizumab before cystectomy (99).

The use of checkpoint-inhibitors for advanced or metastatic UC are established in the clinical practice based on data from two phase III randomized trials (NCT02853305, NCT02302807). Many potential biomarkers to predict response to immunotherapy have been investigated: molecular subtypes, PD-L1 status, TMB, immune infiltration, DNA gene repair status, etc. (100). However, none of these has shown to date enough reproducibility and reliability to be applied alone in the clinical practice and further evidence is needed.

High-throughput molecular profiling of BC and UTUC allowed us to better understand the mechanisms that drive the biology of UC. At clinical, morphological and molecular level, BC seems to represent differences compared to UTUC. Moreover, mutational signatures were repetitively found in different frequencies in BC and UTUC. This is currently not taken into account in clinical practice and UC are treated with only limited distinction of the anatomical location of the tumor.

Conclusions

Taken together, despite similarities of BC and UTUC, clinicopathologic and molecular differences may question to generally assemble both in the same tumor entity.

Treatment standards for UTUC are often adopted from BC. However, a specific investigation in the former may still be meaningful as shown by the example of adjuvant cisplatin based chemotherapy.

Future investigations should prioritize in the understanding of the tumor biology of both. This may reveal which UTUC can be treated according to treatment standards of BC and in which cases, a separate approach may be more appropriate.

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