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Review Article

Diagnostic, Therapeutic and Prognostic Implications of Urothelial Carcinoma, A Review

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ABSTRACT

Urothelial carcinomas are cancerous tumors that can affect both the lower and upper urinary system and develop from the urothelial epithelium. The majority of urinary tract cancers (90–95%) are bladder tumors. UTUCs are rare, making up just 5–10% of UCs and their annual prevalence in Western nations is thought to be close to two instances per 100,000 people. This review of the article gives a general overview of the introduction, classification, diagnostic and therapeutic importance of urothelial carcinoma. About 48 recent publications, suitable for literature review, were retrieved from three different databases: PubMed, Sci. hub, and Google scholar. Careful reading and analysis of the literature review was carried out using inclusion and exclusion criteria. Despite significant improvements in prognosis and treatment, such as surgical methods, different adjuvant therapies, radical cystectomy, and robot-assisted radical cystectomy, tumors still recur with a dismal 5-year survival rate, making the addition of novel target-based therapies necessary to improve the overall outcome. Future treatments targeting genomic changes and the immune system should be tailored to each person's molecular profile. The majority of cases of urothelial carcinoma have been linked to numerous risk factors. For individuals with metastatic urothelial cancer, which includes bladder cancer and cancers of the upper urinary tract and urethra, numerous therapy options have been made available recently. These include targeted therapies and immunotherapy. This review recommended the possible way for diagnostic, therapeutic and prognostic implications of urothelial carcinoma.

INTRODUCTION

The mucosal surface epithelium that borders the ureter, bladder, and urethra as well as the calyces, pelvis, and urinary collecting tubules is referred to as "urothelium." The urothelium, the tissue that lines a section of the urinary tract, is the birthplace of the cancer known as urothelial carcinoma. Urothelial carcinoma is the primary cause of 90% of all occurrences of bladder cancer and 7% of all cases of kidney cancer, including renal pelvis cancer and cancer of ureter [1]. Urothelial carcinomas of the bladder and kidney have similar symptoms. They both have similar prognoses in that they are easily treatable when discovered early on but frequently recur. Urothelial carcinoma, formerly known as transitional cell carcinoma. In the USA, urothelial carcinoma is the most prevalent form of bladder cancer [2]. The fourth most frequent type of tumors are urothelial carcinomas (UCs) [3]. Urothelial carcinoma have different types as they can be found in the upper urinary tract which are mostly pyelocaliceal cavities and ureter and may be present in the lower urinary tract which mostly consists of bladder and urethra. The majority of urinary tract cancers (90–95% of UCs) are bladder tumors. UTUCs are rare, making up just 5–10% of UCs, and their annual prevalence in Western nations is thought to be close to two instances per 100,000 people. Pyelocaliceal tumors are almost two times more frequent than ureteral tumors. Concurrent bladder cancer is found in 17% of

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patients [3].

Urinary Bladder Cancer

The bladder is an organ in the lower abdomen that is primarily responsible for storing urine that has been collected from the kidneys via the ureters until urination [4]. Many mutagens, which the kidneys filter before they reach the bladder, are continuously exposed to bladder cells. Urine is stored in the bladder's urothelial cells, which are transitional epithelial cells [5-7]. Urothelial carcinoma has two unique subgroups from a pathological perspective: muscle-invasive BC and non-muscle-invasive BC (MIBC). Non-muscle invasive: This describes bladder cancer that has progressed beyond the bladder but not to the muscles. Muscle-invasive: This bladder cancer has penetrated the muscle that lines the bladder wall and may have migrated to nearby organs or to fatty layers or tissues there [8, 9]. 75–80% of cases of urothelial carcinoma are caused by NMIBC. It is a subtype that often poses little risk to the patient's life. Nonetheless, it could often have a high recurrence rate, necessitating lifelong monitoring [10]. The European Union is home to nine of the top 20 countries with the highest frequency of BCa, with Belgium having the highest rate (17.5 per 100 000 age-standardized) [11]. The most expensive type of cancer to treat is BCa, per patient, costing $4.25 billion annually in the USA and £55.39 million annually in the UK [12, 13]. UBCs are typically discovered in older people, with a median age at diagnosis of sixty nine years for males and seventy three years for women. Bladder cancer was the 8th most common disease in men and the seventeenth most common cancer in women in Japan in 2009. Age-standardized incidence rates of bladder cancer were 8.6 for males and 1.8 for women (reference population: world population). Starting in 1985, the incidence rate for men was 12.7 and for women was 2.7 (standard population) in the Japanese model population. Men were 4.7 times more likely than women to have bladder cancer [14, 15].

Risk Factors of Urothelial Bladder Cancer

Numerous urothelial bladder cancer risk factors have been identified through investigations; the two most significant are smoking and certain occupational exposures [16]. Bladder cancer is caused by carcinogenic substances found in cigarettes; however, these substances have not been definitively identified. Smoking is known to alter the DNA damage response system, which may heighten or lessen the host's defense against carcinogens. Cigarettes include more than 60 recognized carcinogens and reactive oxygen species [17]. The risk of developing BC is continuously rising with the amount of cigarettes and years smoked, and is three times greater in past smokers and almost six times higher in current smokers compared to never smokers [18]. Alcohol consumption among dietary components tends to contribute to the pathogenesis of BC, although vitamin D intake and regular consumption of fruits and vegetables may have a preventive impact [19]. The relative risks for bladder cancer for all smokers, current smokers, and past smokers were 2.62 (95% CI 2.43-2.83), 3.49 (95% CI 3.13-3.88), and 2.07 (95% CI 1.84-2.33), respectively, according to a meta-analysis that included data from 88 studies. The frequency of smoking may have an impact on the severity of bladder cancer. Addicted smokers (30 pack years) were more likely than non-smokers to have a high-grade malignancy and a muscle-invasive illness at their initial presentation in a study of 740 individuals diagnosed during a 20-year period [20]. In a study four hundred plus six patients who were facing a cancer (muscle-invasive bladder) who were enrolled in the Cancer Genome Atlas study, Wilcox *et al.*, looked into the associations between smoking status, typical adult jobs, and the time to UBC recurrence. UBC recurrence increases when smoking rate increases and they also invented that occupation of a person also somehow linked to the risk of muscle-invasive bladder cancer [21]. The main cause of bladder cancer is schistosoma haematobium infection, which is most common in East Africa and the Middle East. Due to public health initiatives, the prevalence of schistosomiasis has significantly decreased in Egypt, which has seen a decrease in the incidence rate of schistosomal bladder cancer [16]. Diabetes mellitus is treated with thiazolidinediones, which are oral hypoglycemic drugs. According to preliminary research, using these drugs frequently is associated with an increased risk of bladder cancer. An OR for pioglitazone in the randomized clinical trials was found to be 2.51 (95% CI 1.09-5.80) and an OR for "ever" users versus non-users in observational studies to be 1.21 (95% CI 1.09-1.35) in the meta-analysis of 18 studies (five randomized clinical trials with almost 7900 participants and 13 observational studies with more than 2.6 million patients) [16, 22]. The overall relative risk brought on by occupational exposures ranges from 1.2 to 1.4. Employees in the rubber and chemical industries who are exposed to aromatic amines face a significant occupational cancer risk. Recurrent urological screenings were performed on dyestuff workers exposed to benzidine, beta-naphthylamine, alpha-naphthylamine, and dianisidine to assess the frequency of urothelial carcinoma [23]. According to site-specific cancer mortality research, people who made or created beta-naphthylamine had a far higher risk of developing bladder cancer than those who were exposed to alpha-naphthylamine [16]. Numerous epidemiological research has looked into the role that genetic risk factors may have in the emergence of UBC. In the majority of these studies, it was discovered that family members of bladder cancer patients had a slightly higher risk of contracting the illness

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themselves. Those with affected relatives who received a diagnosis prior to the age of 60 appear to be at the greatest risk. 65 families in the Swedish Family History Cancer Database had a parent-child pair diagnosed with bladder cancer between 1958 and 1996. Children of bladder cancer patients have an increased risk of developing the disease (standardized incidence ratios for sons and daughters are 1.35 and 2.29, respectively)[16].

Bladder Cancer Treatment

The five year overall survival (OS) rate for metastatic illness is 15%, and although early detection and multimodality therapy have a good effect on the outcomes of patients, metastatic disease is frequently incurable. The FDA's clearance of five immune checkpoint medicines has significantly altered the treatment options available for advanced UBC, even if platinum-based chemotherapy is still the standard of care. Immunotherapeutic antibodies that target PD-1 and its ligand (PD-L1) are now widely used in clinical settings after decades of dismal trial outcomes in metastatic UC. Exceptionally, a phase 3 trial found that pembrolizumab was superior to chemotherapy in terms of OS and quality of life [24]. Due to this discovery, ICIs have replaced single-agent chemotherapy as the second-line therapy, and a commensurate number of patients have shown sustained responses. Both cisplatin-eligible and cisplatin-ineligible populations, such as elderly patients and those with low performance status, should consider ICIs as a viable alternative due to their acceptable safety profile. Although ICIs have been made available to PD-L1 positive patients with metastatic UC who are not candidates for platinum therapy and are ICI-eligible, no prospective study evaluating the best front-line therapeutic option has been finished. Ervafitinib, an oral drug that targets the pan-fibroblast growth factor receptor (FGFR), has received expedited approval from the FDA as a result of relevant clinical activity in metastatic UC patients with tumors that have treatable FGFR mutations [24-26]. Enfortumab vendotin, an antibody-drug combination that targets nectin, has also been recognised by the FDA as a breakthrough treatment for people with locally advanced or metastatic UC who have previously taken ICIs. Large cohorts of UC patients have been the subject of comprehensive studies, and whole-genome characterization of tumors has been carried out. As a result, scientists now have more accurate knowledge about how frequently genetic alterations occur and how these changes impact treatment outcomes. The discovery that PPAR high/RXR S427F/Y suppresses CD8+ T-cell infiltration underpins MIBC resistance to ICIs or the identification of a subset of UCs with FGFR genetic alterations, for example, both led to the creation of FGFR inhibitors [27-29].

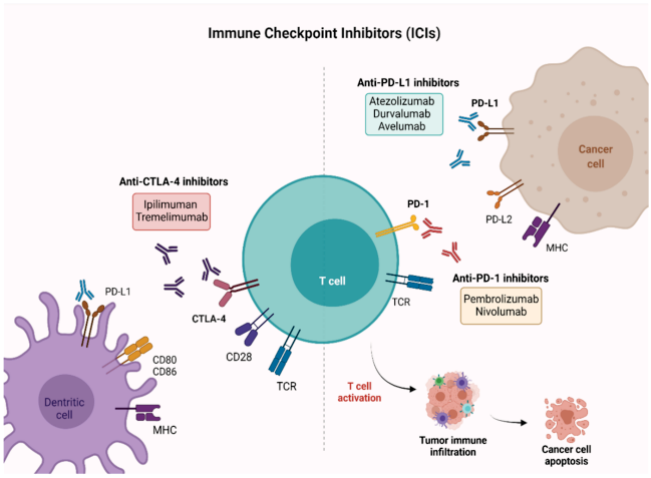

Figure 1: Shows the mechanisms through which ICIs that target PD-1, PD-L1, and CTLA-4 work. T cells that have been activated express the proteins PD-1 and CTLA-4. They inhibit the death of tumor cells by inactivating T lymphocytes by attaching to the corresponding ligands that are present on the surface of cancer cells.

Immune checkpoint blockage makes sure that T cells are activated and encourages anticancer activity [24]

The gold standard of care for people with muscle-invasive bladder cancer (MIBC) has been neoadjuvant chemotherapy using the medication cisplatin, followed by a radical cystectomy [30]. After neoadjuvant treatment, patients with clinically localized MIBC have better overall survival, according to research [31]. Additionally, chemotherapy administered in a neoadjuvant setting enables pathological examination of the tumor tissue removed from the patient to track pre- and postoperative cancer response. The PD-1 pathway can affect T cell priming towards cancer antigens in secondary lymphoid organs and is important for local immunosuppression in the tumor microenvironment (TME) [32]. Scientific evidence backs up two alternative theories of powerful anticancer activity in the neoadjuvant setting. First, anti-PD-(L)1 stimulates the proliferation, trafficking, and rejuvenation of tumor-specific cytotoxic T lymphocytes in the tumor bed. Second, the anti-PD-(L)1 promotes systemic antitumor immunity by improving tumor antigen presentation by dendritic cells to naive T cells in tumor-draining lymph nodes [33]. Due to the effectiveness of immune checkpoint therapy in advanced UC and the precedent set by the neoadjuvant approach to conventional chemotherapy, there is a lot of interest in exploring the potential role of neoadjuvant ICB in MIBC [34]. In a number of early-phase clinical trials, neoadjuvant ICB alone or in conjunction with radical cystectomy has produced favorable outcomes for bladder cancer patients [21]. Numerous important preclinical investigations have suggested that neoadjuvant ICB may increase long-term

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survival in experimental bladder cancer animals [35]. Here, we go over the key findings of early phase I/II trials examining intraoperative chemotherapy (ICB) and the rationale for employing neoadjuvant immunotherapy in localized bladder cancer from a preclinical perspective [36].

Upper Tract Urothelial Cancer

Upper tract urothelial carcinomas (UTUC), a rare and heterogeneous disease with an estimated frequency in the US of 2.08 cases per 100,000 person-years, account for around 5% of all urothelial malignancies. Upper tract urothelial cancers (UTUCs) usually occur in the lining of the ureter or kidney due to which people suffering from UTUC feel pain in the upper abdomen, middle of back and near kidneys. Severity in UTUC may also cause hydronephrosis (kidney or ureter blockage) or even impairment of kidney function. Like bladder cancer, UTUCs can present as low- or high-grade tumors. Low-grade tumors are not frequently invasive and seldom, if ever, spread outside of the kidney or ureter. However, once it has spread from the kidney or ureter, high-grade UTUC may affect the lymph nodes, the lung, and the bone [37]. UTUC of high grade is comparatively more aggressive over the low grade. Invasive procedures are needed to be adopted in the majority of the UTUC cases diagnosed. Recent developments in imaging and endoscopic techniques, as well as improvements in bladder cancer (BCa) control results, have led to stage migration towards earlier-stage tumors. In some studies, diagnosis revealed two-thirds of UTUCs as invasive in contrast to 15–25% of bladder tumors [38]. Males are three times more susceptible to have UTUC as compared to females, and the high prevalence of UTUC has been observed in the patients of old age (70 to 90 years). The incidence of the development of muscle-invasive bladder cancer is 3-5% more in the patients who have undergone radical cystectomy. In hereditary nonpolyposis colorectal cancer, UTUCs are connected to familial/hereditary UTUCs [39]. Doctors use a diagnostic standard, The Amsterdam criteria, to diagnose families susceptible to Lynch syndrome carriers [5]. The Immunohistochemistry studies on UTUC associated with Lynch revealed that among 98% of the samples (46% of which had microsatellite instability and 54% of which had stability), a decrease in protein expression consistent with the disease-predisposing mismatch was observed. Patients at suspected high risk of Lynch syndrome should be subjected to DNA testing followed by family counselling. Several environmental factors are linked with the emergence of UTUC [6, 7]. None of the other components, including smoking and aristolochic acid, have any published data to support their causality. When exposed to cigarettes, the relative risk rises from 2.5 to 7 [7]. UTUC are also termed as amino tumors in some studies which have linked the incidence of UTUC with the exposure to benzidine and b-naphthalene, the carcinogenic aromatic amines. Both of these amines have been banned in several industrial sectors in many countries since 1960. However, the typical exposure time required to develop UTUC is quite long i.e., 7 years with a 20-year latency period. There has been conjecture that Taiwan's high water arsenic levels may be due to UTUC, which comprises 20–25% of the local UCs [40]. Several other chemicals are also reported to be associated with UTUC such as aristolochic acid. It is a nitro phenanthrene carboxylic acid poses mutations in p53 gene at 139 codon resulting into the development of UTUC Despite the fact that the prevalence of Balkan endemic nephropathy is also decreasing, aristolochic acid and Chinese herb use have been linked to the pathogenesis and induction of this nephropathy, respectively. The ability of the body to fight off carcinogens may differ from person to person. Certain genetic polymorphisms cause variation in how each person is susceptible to the risk factors mentioned above by increasing the risk of cancer or accelerating the course of the disease. There is a possibility that UTUC and bladder UC have similar risk factors or molecular disruption pathways. Two UTUC-specific polymorphisms are now recognised [41].

Computerized Tomography Urography

The most efficient imaging technique for UTUC diagnosis is computed tomography (CT) urography [22]. In a meta-analysis of 1233 patients and 13 trials, the combined sensitivity and specificity of CT urography for UTUC has been reported as 92% (confidence interval [CI]) and 95%, respectively. It is feasible to create high-quality, isotropic images quickly using thin-section capture that may be seen in multiple planes without losing resolution, which can aid in diagnosis. Epithelial "flat lesions" are typically not visible on CT unless there is a bulk effect or urothelial thickening. A consistent indicator of metastatic disease is an increase in LNs in the UTUC [41]. Prior to starting any form of treatment with the intention of healing the ailment, it is imperative to rule out distant metastases [39].

Magnetic Resonance Urography

The patients for whom CT urogram is not appropriate, due to radiation or iodinated contrast media, they are subjected to MR urography. Once contrast is used, MR urography is 75% sensitive for cancers smaller than 2 cm. Due to the possibility of nephrogenic systemic fibrosis, patients with severe renal impairment (30 ml/min creatinine clearance) should employ MR urography with gadolinium-based contrast medium with caution. CT urography is the most often used alternative to MR urography for the diagnosis and staging of UTUC [42].

Cystoscopy and Urinary Cytology

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The diagnosis of UTUC requires urethrocystoscopy in order to exclude concomitant bladder cancer. When a bladder cystoscopy reveals no CIS in the prostatic urethra or bladder and everything seems normal, atypical cytology may be a sign of high-grade UTUC [15, 26, 27]. Cytology should only be done on the upper tract that is affected, despite the fact that it is less sensitive for UTUC than bladder tumors. Finding UTUCs still works well with retrograde ureteropyelography [22, 29, 30]. Urine cytology of the renal canals and ureteral lumina is preferred before using a contrast agent for retrograde ureteropyelography as doing so could cause the cytological materials to deteriorate [30, 31]. A recent study found that barbotage cytology and biopsy histology can both detect up to 91% of malignancies. In a recent study, biopsy histology and barbotage cytology both detected up to 91% of malignancies with identical accuracy [32]. Its usefulness in clinical treatment is still debatable since fluorescence in situ hybridization is only around 50% sensitive to the molecular abnormalities that identify UTUCs [31, 33].

Diagnostic Ureteroscopy

The ureter, renal pelvis, and collecting system can all be seen during flexible ureteroscopy (URS), which is also used to biopsy suspicious lesions. Tumor existence, appearance, and size can all be detected with URS. Tumor existence, appearance, and size can all be detected with URS. Additionally, uretero-scopic biopsies have a low false-negative rate and can reliably detect the malignancy grade in 90% of instances, independent of sample size. Comprehensive follow-up is necessary if a kidney-sparing treatment is chosen because undergrading may occur after the diagnosis biopsy. URS also facilitates selective ureteral sampling for in-situ cytology. It is incorrect to use a ureteroscopic biopsy to assess stage. The grade of the ureteroscopic biopsy, imaging anomalies such as renal-sparing therapy, and radical nephroureterectomy (RNU) selection may all have an impact. The rate of intravesical recurrence following RNU may be higher in patients who received diagnostic URS prior to surgery, according to some studies, however this was not the conclusion of another study [43, 44].

Preoperative Variables Age and gender

Reduced cancer-specific survival (CSS) is independently connected to age at the time of RNU. RNU, however, has the ability to treat individuals of any age. Since this is the case, chronological age should not be a barrier to RNU. The prognosis of UTUC is unaffected by gender.

Ethnicity

A multicenter review of academic centers found no difference in outcomes between races, however US population based research has shown that African-American patients perform worse than patients of other ethnicities. It is unknown if this is due to biological factors, patterns of care, or access to care [45]. Another study has shown variations in risk factors, illness features, and indicators of poor oncological outcomes between Chinese and American patients at presentation. The UC's initial location is a predicting factor in many studies. Once the impact of tumor stage has been taken into account, patients with renal pelvic tumors appear to have a better prognosis than individuals with ureteral and/or multifocal tumors [46].

Surgery Delay

If an invasive tumor is detected later than it is removed, there may be a greater chance that the disease may advance. If at all possible, the RNU procedure should be completed within 12 weeks. A higher American Society of Anesthesiologists score and other Poor Performance Status both lead to worse CSS after RNU. In patients receiving RNU, obesity and a greater body mass index have a negative impact on the results related to the malignancy. Low albumin and a high pretreatment neutrophil-lymphocyte ratio have both been linked to lower cancer-specific mortality [47, 48].

CONCLUSIONS

Nearly 150,000 people worldwide still perish each year from urothelial carcinoma, one of the most common and dangerous diseases. Combination chemotherapy based on cisplatin is still the gold standard of treatment for metastatic urothelial carcinoma as a first-line systemic condition. Despite this, tremendous progress has been made in understanding the genetic underpinnings of urothelial cancers, which opens up a brand-new field of treatment.

Authors Contribution

Conceptualization: SKP
Methodology: B, FI
Formal analysis: SAAZ
Writing-review and editing: FI, UQK, ZAM, SAAZ

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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