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Histopathological Heterogeneity in Upper Tract Urothelial Carcinoma and Bladder: A Systematic Review

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A B S T R A C T

Upper tract urothelial carcinoma (UTUC) and bladder is a rare malignancy with varied histopathological features that influence treatment strategies and patient outcomes. This systematic review comprehensively analyzes the histopathological heterogeneity of UTUC and bladder, focusing on its impact on diagnosis, prognosis, and therapeutic implications. A systematic search of PubMed, Google Scholar, NCBI, and ScienceDirect was conducted to identify relevant studies published in the last 20 years. Articles were included if they focused on the histopathological characterization of UTUC and bladder. A total of 10 studies were included in the review. Histopathological analysis revealed diverse subtypes, including papillary, micropapillary, nested, plasmacytoid, and sarcomatoid variants, each with distinct features and prognostic implications. In conclusion, UTUC and bladder exhibits significant histopathological heterogeneity, which influences tumor behavior and patient outcomes. Integrating histopathological evaluation with molecular profiling can refine risk stratification and guide personalized treatment decisions. Further research is needed to elucidate the complex interplay of these factors and develop targeted therapies for improved management of UTUC and bladder.

1. Introduction

Upper tract urothelial carcinoma (UTUC) and bladder is a relatively rare malignancy, representing about 5-10% of all urothelial carcinomas. It originates from the urothelial cells lining the inner surface of the upper urinary system, encompassing the renal pelvis, ureters, and calyces. While it shares similarities with bladder cancer, UTUC and bladder presents unique challenges due to its anatomical location and distinct clinical behavior. The incidence of UTUC and bladder is on the rise globally, attributed to factors such as improved diagnostic techniques, increased awareness, and an aging population. Studies indicate an annual increase of approximately 3% in certain demographics, underscoring the growing importance of understanding this disease. The incidence of UTUC and bladder varies across different regions and populations, influenced by a complex interplay of risk factors. It is more prevalent in men than women, with a male-to-female ratio ranging from 2:1 to 3:1. Age is a significant risk factor, with most cases diagnosed in individuals over 65 years old. Geographically, areas with high smoking rates tend to have a higher incidence of UTUC and bladder, highlighting the role of environmental exposures. The global age-adjusted incidence rate (ASIR) for UTUC and bladder is estimated to be around 5-15% of all genitourinary malignancies. However, regional variations exist, with

certain countries reporting higher ASIRs due to specific risk factors such as schistosomiasis and occupational exposures.[1-3]

UTUC and bladder often presents with nonspecific symptoms, including hematuria, flank pain, and abdominal mass. This often leads to delayed diagnosis, as these symptoms can mimic other urological conditions. The diagnosis of UTUC and bladder typically involves a combination of imaging techniques, such as computed tomography (CT) urography, magnetic resonance imaging (MRI), and retrograde pyelography, along with cystoscopy and ureteroscopy for direct visualization and biopsy. Urine cytology may also be used to detect malignant cells, but its sensitivity can be limited. Histopathological evaluation of UTUC and bladder is crucial for accurate diagnosis, subtyping, and prognostication. The most common histological subtype is urothelial carcinoma, which can be further categorized into low-grade and high-grade tumors based on cellular atypia, mitotic activity, and architectural features. However, UTUC and bladder exhibits significant histopathological heterogeneity, with various subtypes displaying distinct features and clinical implications. These subtypes include; Papillary urothelial carcinoma: Characterized by finger-like projections into the lumen of the upper urinary tract; Micropapillary urothelial carcinoma: A rare and aggressive subtype with micropapillary architecture resembling ovarian papillary serous tumors; Nested urothelial carcinoma: Characterized by nests of tumor cells infiltrating the stroma; Plasmacytoid urothelial carcinoma: Composed of cells with abundant cytoplasm resembling plasma cells; Sarcomatoid urothelial carcinoma: A high-grade subtype with spindle cells or sarcoma-like features.[4-6]

The stage and grade of the tumor are the most important prognostic factors for UTUC and bladder. However, other factors, such as tumor location, histological subtype, lymphovascular invasion, and lymph node involvement, can also influence survival. The presence of variant histological subtypes, such as micropapillary and sarcomatoid, is often associated with more aggressive tumor behavior and worse prognosis. The mainstay of treatment for UTUC is radical nephroureterectomy (RNU), which involves the surgical removal of the kidney, ureter, and a portion of the bladder cuff. This procedure aims to achieve complete tumor removal and prevent local recurrence and distant metastasis. However, RNU is a major surgical procedure with potential complications, such as bleeding, infection, and urinary tract obstruction. Adjuvant chemotherapy may be considered for patients with high-grade tumors or variant subtypes to reduce the risk of recurrence and improve survival. However, the optimal chemotherapy regimen and the selection of patients who would benefit most from adjuvant therapy remain areas of ongoing research.[7,8]

The management of UTUC and bladder faces several challenges, including delayed diagnosis, limited treatment options, and poor prognosis for advanced disease. Further research is needed to improve early detection strategies, develop more effective therapies, and identify biomarkers for risk stratification and personalized treatment. Recent advances in molecular profiling have provided insights into the genetic alterations driving UTUC and bladder development and progression. These alterations can influence tumor behavior, response to therapy, and patient outcomes. Integrating molecular data with histopathological evaluation can refine risk stratification and guide personalized treatment decisions.[9,10]

Immunotherapy has emerged as a promising treatment approach for various cancers, including UTUC and bladder. Immune checkpoint inhibitors, such as pembrolizumab and nivolumab, have shown encouraging results in clinical trials for patients with advanced UTUC and bladder. However, further research is needed to optimize the use of immunotherapy and identify biomarkers for predicting response. Targeted therapies, such as fibroblast growth factor receptor (FGFR) inhibitors and mammalian target of rapamycin (mTOR) inhibitors, are being investigated for the treatment of UTUC and bladder. These therapies target specific molecular alterations driving tumor growth and may offer new

treatment options for patients with advanced or recurrent disease.[11,12] This systematic review aims to comprehensively analyze the histopathological heterogeneity of UTUC and bladder, focusing on its impact on diagnosis, prognosis, and therapeutic implications. By synthesizing the available evidence, we aim to provide a comprehensive overview of the current understanding of UTUC and bladder histopathology and its clinical significance.

2. Methods

A systematic and comprehensive search strategy was implemented to identify relevant studies investigating the histopathological heterogeneity of UTUC and bladder. The following electronic databases were meticulously searched; PubMed; Google Scholar; NCBI; ScienceDirect. These databases were selected for their extensive coverage of biomedical literature, ensuring the inclusion of a wide range of relevant studies. The search strategy was carefully crafted using a combination of keywords and medical subject headings (MeSH terms) relevant to UTUC and bladder and histopathology. The following keywords were employed; "upper tract urothelial carcinoma"; "UTUC and bladder"; "histopathology"; "histological subtypes"; "prognosis"; "treatment". These keywords were combined using Boolean operators (AND, OR) to refine the search and capture all relevant articles. The search was limited to articles published in the last 20 years (2004-2024) to ensure the inclusion of contemporary research reflecting current understanding and practices. In addition to the electronic database search, a manual search of the reference lists of included articles and relevant reviews was conducted to identify any potentially eligible studies that may have been missed during the initial search. This step ensured the comprehensiveness of the literature search and minimized the risk of publication bias.

To maintain the focus and relevance of the systematic review, strict inclusion and exclusion criteria were applied. Articles were included if they met the following criteria; Published in English: This criterion ensured that the included studies were accessible to a wide audience and facilitated data extraction and analysis; Focused on the histopathological characterization of UTUC and bladder: Studies primarily investigating the histological subtypes, their frequencies, and associated features were included; Included original data or provided a comprehensive review of the topic: Original research articles, including observational studies, cohort studies, and case series, as well as comprehensive review articles, were considered for inclusion. Conversely, articles were excluded if they met any of the following criteria; Not related to UTUC and bladder: Studies focusing on other urological malignancies or non-urothelial cancers were excluded; Did not focus on histopathology: Articles primarily addressing clinical presentation, diagnosis, or treatment without a significant emphasis on histopathological features were excluded; Published in a language other than English: This criterion ensured consistency and facilitated data extraction; Editorials, letters to the editor, or case reports: These publication types were excluded due to their limited scope and potential for bias.

The study selection process was conducted in a systematic and stepwise manner to ensure objectivity and minimize bias. The following steps were involved; Identification: The initial search of electronic databases and manual search of reference lists yielded a pool of potentially relevant articles; Screening: Titles and abstracts of identified articles were screened independently by two reviewers to assess their eligibility based on the inclusion and exclusion criteria. Any disagreements were resolved through discussion and consensus; Eligibility: Full-text articles of potentially eligible studies were retrieved and assessed independently by two reviewers to confirm their inclusion based on the predefined criteria. Discrepancies were resolved through discussion and, if necessary, consultation with a third reviewer; Inclusion: Articles that met all inclusion criteria and did not meet any exclusion criteria were included in the systematic review.

Data from the included studies were extracted and compiled into a standardized data extraction form. The following information was extracted; Study characteristics: Author and year of publication, study design, country of origin, and sample size; Histopathological data: Histological subtypes and their frequencies, including papillary, micropapillary, nested, plasmacytoid, and sarcomatoid variants; Clinical and prognostic data: Tumor stage, grade, lymphovascular invasion, lymph node involvement, and survival outcomes; Treatment data: Type of surgery (RNU or other), use of adjuvant chemotherapy, and treatment outcomes. The extracted data were synthesized and analyzed to provide a comprehensive overview of the histopathological heterogeneity of UTUC and bladder and its clinical implications. Due to the anticipated heterogeneity of study designs and outcome measures, a meta-analysis was not deemed appropriate. Instead, a narrative synthesis of the findings was performed, focusing on the key themes and patterns emerging from the included studies.

The quality of the included studies was assessed using appropriate tools based on their study design. Observational studies were assessed using the Newcastle-Ottawa Scale (NOS), which evaluates the selection of study groups, comparability of groups, and ascertainment of outcomes. Review articles were assessed using the Assessment of Multiple Systematic Reviews (AMSTAR) tool, which evaluates the methodological quality of systematic reviews. The quality assessment was conducted independently by two reviewers, and any disagreements were resolved through discussion and consensus. The quality assessment findings were used to interpret the results of the systematic review and to identify potential sources of bias. This systematic review did not involve any human subjects or primary data collection. Therefore, ethical approval was not required. However, all data were extracted and analyzed in accordance with ethical principles and guidelines for research integrity.

3. Results and Discussion

Figure 1 illustrates the process of study selection for this systematic review, adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The process began with a broad identification search across four databases (PubMed, Google Scholar, NCBI, and ScienceDirect), yielding an initial pool of 30,057 articles. After removing duplicates, 12,547 articles remained. These were further screened based on the year of publication, with 8,612 articles excluded for not meeting the 20-year inclusion window (2004-2024). The remaining 3,935 articles underwent title and abstract screening, resulting in the exclusion of 3,824 articles that did not align with the review's focus on histopathological heterogeneity in UTUC AND BLADDER. Of the 111 articles that remained, 12 were excluded due to incomplete text availability. The full texts of the remaining 99 articles were critically appraised for their relevance and methodological rigor, leading to the exclusion of 89 articles. This rigorous selection process ultimately resulted in 10 eligible articles that were included in the final systematic review. This figure highlights the systematic and comprehensive approach taken to identify and select relevant studies, ensuring that the review is based on a robust and reliable evidence base.

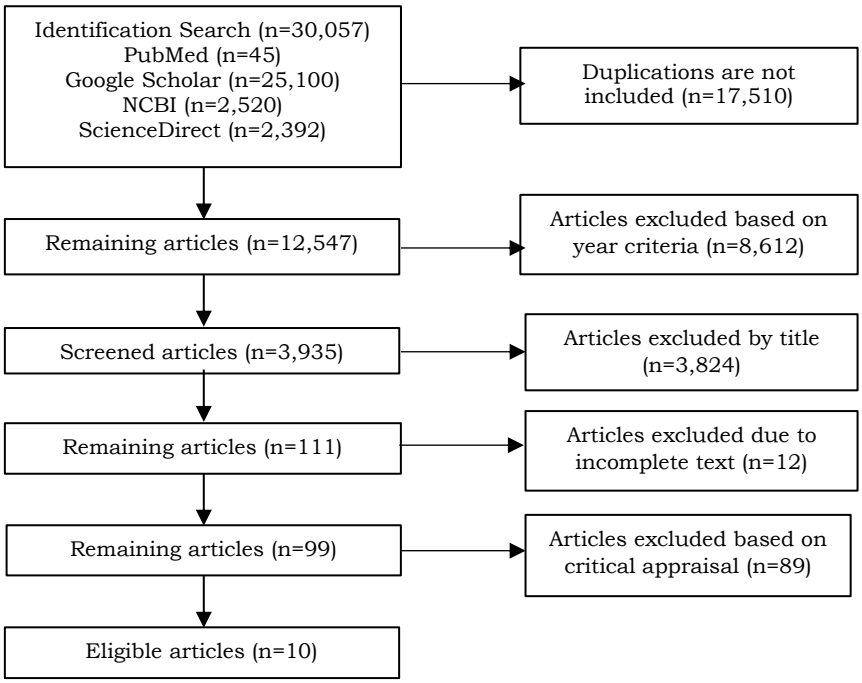

Figure 1. Study selection.

Table 1 provides a comparative overview of different cancer types identified in the upper urinary tract and bladder, as reported in 10 research studies. These studies, conducted between 2005 and 2021, encompass varying sample sizes, ranging from 114 to 1,460 patients. Notably, several studies focused solely on bladder cancer, highlighting the relative rarity of upper urinary tract cancers. The table reveals a diverse array of cancer subtypes, including papillary, micropapillary, squamous, and sarcomatoid variants, among others. The specific subtypes and their prevalence vary considerably across the studies, reflecting the heterogeneity of these cancers. For instance, Giudici et al. (2021) identified six distinct subtypes of bladder cancer, while Rink et al. (2012) reported seven subtypes of upper urinary tract cancer. Interestingly, some studies, such as Cosentino et al. (2013), investigated the concurrence of bladder and upper urinary tract cancers, suggesting a potential link between these malignancies. Other studies, like Zamboni et al. (2019) and Langner et al. (2006), delved into the prognostic implications of different subtypes, highlighting the importance of histopathological characterization for treatment planning.

Upper tract urothelial carcinoma (UTUC) and bladder is not a monolithic disease. It is characterized by a striking degree of histopathological heterogeneity, meaning that the tumors can exhibit a wide range of appearances under the microscope. This heterogeneity is not merely an academic curiosity, it has profound implications for how these tumors behave, how they respond to treatment, and ultimately, how patients fare. Urothelial carcinoma stands as the most prevalent histological subtype within the realm of upper tract urothelial carcinoma (UTUC) and bladder. Originating from the urothelial cells that line the urinary tract, this subtype encompasses a spectrum of tumors, each with varying degrees of aggression and clinical implications. While seemingly uniform in origin, urothelial carcinoma exhibits remarkable diversity, broadly classified into low-grade and high-grade tumors. This distinction holds profound significance in understanding the behavior, prognosis, and treatment strategies for UTUC and bladder.

Table 1. Different types of cancer in the upper urinary tract and bladder.

No.	Author, year	Number of research subjects	Research results	
			Upper urinary tract	Bladder
1.	Giudici et al., 2021[8]	114 patients	-	Papillary luminal (LumP, 24%), nonspecific luminal (LumNS, 8%), unstable luminal (LumU, 15%), stroma-rich (15%), basal/squamous (Ba/Sq, 35%), and neuroendocrine-like (NE-like, 3%).
2.	Stewart et al., 2005[6]	164 patients	Low-grade superficial (47%), low-grade deeply invasive (10%), high-grade superficial (4%), high-grade deeply invasive (40%),	Low-grade superficial (56%), low-grade deeply invasive (10%), high-grade superficial (6%), high-grade deeply invasive (28%),
3.	Cosentino et al., 2013[9]	450 patients	It was found in 90, 82, and 68% of patients with primary cervical/renal UUT-UCC of the pelvis, upper ureter, or lower ureter, respectively.	It was found in 10, 18, and 33% of patients with primary cervical/renal UUT-UCC of the pelvis, upper ureter, or lower ureter, respectively.
4.	Rink et al., 2012[10]	398 patients	Squamous cell (9.9%) Glandular (4%) Sarcomatoid (2.4%) Micropapillary (1.9%) Small cell (1.9%) Plasmacytoid (0.2%) and Multiple (3.9%)	-
5.	Zamboni et al., 2019[11]	1,460 patients	Cases of micropapillary 89 (5.0%), squamous 41 (2.0%), sarcomatoid 10 (1.0%), and other tumors 10 (1.0%)	-
6.	Langner et al., 2006[12]	268 patients	Nodular pattern 7%, trabecular pattern 23%, infiltrative pattern 79%, urothelial differentiation 33%, squamous differentiation 58% and glandular differentiation 53%.	-
7.	Rolim et al., 2020[13]	115 patients	Squamous 7%, sarcomatoid 6%, glandular 4%, inverted growth 3%, micropapillary 3%, clear cell glycogenic 3%, plasmacytoid 3%, lipid-rich 3%, pseudoangiosarcomatous 2%, nested 1%, giant 1%, lelc 1%, small cell 1%, trophoblastic 1%, rhabdoid 1%, microcystic 1%, lymphoid-rich stroma 1% and myxoid stroma/chordoid 1%.	-
8.	Wasco et al., 2007[14]	743 patients	-	Squamous (40%) and glandular (18%)
9.	Shinagare et al., 2011[15]	150 patients	-	Transitional cell carcinoma group 94 (63%) patients and atypical histologic features group 56 (37%) patients.
10.	Xylinas et al., 2013[16]	488 patients	-	Pure urothelial carcinoma 75.4%, urothelial carcinoma variant 24.6%, squamous cell differentiation 11.4%, glandular differentiation 3.8%, sarcomatoid differentiation 2.0%, micropapillary differentiation 1.7%, small cell differentiation 2.0%, plasmacytoid differentiation 0.4% and multiple variant differentiation 3.3%.

Low-grade urothelial carcinomas represent a less aggressive form of UTUC and bladder. They are characterized by a more indolent growth pattern and a reduced propensity for invasion and metastasis. Histologically, these tumors often exhibit a papillary architecture, forming finger-like projections that extend into the lumen of the urinary tract. This exophytic growth pattern contributes to their less invasive nature, as they tend to remain confined to the mucosal layer without penetrating deeply into the surrounding tissues. The cytological features of low-grade urothelial carcinomas further underscore their less aggressive nature. The tumor cells generally maintain a relatively normal appearance, with minimal nuclear atypia and infrequent mitotic figures. This indicates a slower rate of cell division and a reduced likelihood of acquiring additional genetic alterations that could drive further progression. Recent advances in molecular profiling have shed light on the genetic underpinnings of low-grade urothelial carcinomas. These tumors frequently harbor mutations in genes involved in the regulation of cell

growth and differentiation, such as FGFR3 and PIK3CA. These mutations are thought to contribute to the development and progression of low-grade tumors, albeit at a slower pace compared to their high-grade counterparts. The less aggressive nature of low-grade urothelial carcinomas translates into a more favorable prognosis for patients. These tumors are less likely to recur or metastasize, resulting in improved long-term survival outcomes. However, it is essential to acknowledge that low-grade tumors can still progress to high-grade lesions if left untreated or inadequately managed. In contrast to their low-grade counterparts, high-grade urothelial carcinomas represent a more aggressive form of UTUC and bladder. They are characterized by rapid growth, increased invasiveness, and a higher propensity for metastasis. Histologically, these tumors often exhibit a more solid or infiltrative growth pattern, invading deeply into the underlying muscle layer and beyond. The cytological features of high-grade urothelial carcinomas reflect their aggressive nature. The tumor cells display marked nuclear atypia, with enlarged and irregular nuclei, prominent nucleoli, and frequent mitotic figures. This indicates a higher rate of cell division and an increased likelihood of accumulating further genetic alterations that can fuel their malignant potential. Molecular profiling studies have revealed distinct genetic alterations in high-grade urothelial carcinomas. These tumors often harbor mutations in genes involved in cell cycle control, DNA repair, and tumor suppression, such as TP53, RB1, and PTEN. These alterations contribute to their aggressive behavior and resistance to conventional therapies. The aggressive nature of high-grade urothelial carcinomas poses significant challenges in their management. These tumors are more likely to recur and metastasize, resulting in poorer long-term survival outcomes. Early detection and prompt intervention are crucial to improving the prognosis for patients with high-grade UTUC and bladder. Beyond the conventional low-grade and high-grade urothelial carcinomas, a group of less common but more aggressive subtypes exists within the spectrum of upper tract urothelial carcinoma (UTUC) and bladder. These variant subtypes, though rare, pose significant challenges due to their aggressive nature and poorer prognosis. Their unique histopathological features often deviate from the conventional urothelial carcinoma, requiring meticulous examination and accurate diagnosis for appropriate management. Micropapillary urothelial carcinoma is a rare variant subtype characterized by a distinctive micropapillary architecture. The tumor cells arrange themselves in small, delicate papillary structures, reminiscent of ovarian papillary serous tumors. This unique morphology sets it apart from the conventional papillary urothelial carcinoma, which typically exhibits larger, more robust papillary formations. The aggressive nature of micropapillary UTUC and bladder is evident in its propensity for early invasion. Unlike low-grade urothelial carcinomas that tend to remain confined to the mucosal layer, micropapillary UTUC and bladder often presents with muscle-invasive disease at the time of diagnosis. This early invasion signifies its ability to penetrate deeply into the surrounding tissues, increasing the risk of local recurrence and distant metastasis. The prognosis for patients with micropapillary UTUC and bladder is generally poor, underscoring the need for prompt and aggressive treatment. The 5-year survival rate for patients with this variant subtype is significantly lower compared to those with conventional urothelial carcinoma. This dismal prognosis highlights the importance of accurate diagnosis and timely intervention to improve patient outcomes. Nested urothelial carcinoma is another variant subtype that presents diagnostic challenges due to its unique morphology. In this variant, the tumor cells are arranged in nests or clusters within the stroma, the connective tissue surrounding the tumor. This nested pattern can mimic benign conditions such as nephrogenic metaplasia, potentially leading to misdiagnosis or delayed diagnosis. Accurate diagnosis of nested UTUC and bladder is crucial, as it can behave aggressively despite its deceptively benign appearance. The tumor cells may infiltrate the surrounding tissues, increasing the risk of local

recurrence and distant metastasis. Therefore, pathologists must exercise vigilance in identifying the subtle cytological features that distinguish nested UTUC and bladder from benign mimics. Plasmacytoid urothelial carcinoma is a variant subtype characterized by its abundant cytoplasm, resembling plasma cells. This distinctive morphology sets it apart from the conventional urothelial carcinoma, which typically exhibits less abundant cytoplasm. The aggressive nature of plasmacytoid UTUC and bladder is reflected in its rapid growth and propensity for metastasis. The tumor cells often display marked nuclear atypia and frequent mitotic figures, indicating a high rate of cell division and an increased likelihood of accumulating further genetic alterations that can fuel their malignant potential. The prognosis for patients with plasmacytoid UTUC and bladder is generally worse compared to those with conventional urothelial carcinoma. This underscores the importance of accurate diagnosis and timely intervention to mitigate the risk of disease progression and improve patient outcomes. Sarcomatoid urothelial carcinoma is a high-grade variant subtype that exhibits features of a sarcoma, a type of cancer that arises from connective tissues. The presence of spindle cells, elongated cells resembling connective tissue cells, is a hallmark of this variant subtype. The aggressive nature of sarcomatoid UTUC and bladder is evident in its rapid growth, extensive invasion, and propensity for metastasis. The tumor cells often display marked nuclear atypia and frequent mitotic figures, indicating a high proliferative rate and an increased likelihood of acquiring further genetic alterations that can drive their malignant potential. Due to its highly malignant nature, sarcomatoid UTUC and bladder often requires a multimodal treatment approach, including surgery, chemotherapy, and radiation therapy. The prognosis for patients with this variant subtype is generally poor, highlighting the need for aggressive treatment strategies to improve patient outcomes. The clinical significance of histopathological heterogeneity in upper tract urothelial carcinoma (UTUC) and bladder cannot be overstated. It plays a pivotal role in guiding treatment decisions, predicting patient prognosis, and ultimately shaping the course of the disease. Recognizing and understanding the diverse subtypes of UTUC and bladder is paramount for clinicians to provide tailored care and optimize patient outcomes. The histopathological subtype of UTUC and bladder serves as a crucial guide in determining the appropriate treatment strategy. Different subtypes exhibit varying degrees of aggression and response to therapy, necessitating individualized treatment plans. Patients with low-grade urothelial carcinoma, characterized by less aggressive features, may be effectively treated with surgery alone.

Radical nephroureterectomy (RNU), the surgical removal of the kidney, ureter, and a portion of the bladder cuff, is often sufficient to achieve complete tumor eradication and prevent recurrence. In contrast, patients with high-grade urothelial carcinoma, known for its aggressive nature, often require multimodal therapy. RNU remains the cornerstone of treatment, but it is often combined with adjuvant chemotherapy to eliminate any residual cancer cells and reduce the risk of recurrence. The treatment of variant subtypes, such as micropapillary, nested, plasmacytoid, and sarcomatoid UTUC and bladder, poses unique challenges due to their aggressive behavior and poorer prognosis. RNU remains the primary treatment modality, but the role of adjuvant therapy is less well-defined. Clinical trials are ongoing to evaluate the efficacy of various chemotherapy regimens and novel therapies, such as immunotherapy and targeted therapy, in improving outcomes for patients with variant subtypes. The histopathological subtype of UTUC and bladder provides valuable prognostic information, helping clinicians predict patient outcomes and guide treatment decisions. Patients with low-grade urothelial carcinoma generally have a favorable prognosis, with a lower risk of recurrence and metastasis compared to those with high-grade or variant subtypes. High-grade urothelial carcinoma is associated with a worse prognosis, with a higher likelihood of recurrence and metastasis. Variant

subtypes, such as micropapillary and sarcomatoid UTUC and bladder, are particularly aggressive and carry a poorer prognosis. Patients with these subtypes often experience early recurrence and metastasis, resulting in lower survival rates. The prognostic information derived from histopathological subtyping is crucial for informing patients about their expected outcomes and empowering them to participate in shared decision-making regarding their treatment plan.

Understanding the subtype of UTUC and bladder and its associated prognosis allows patients to weigh the risks and benefits of different treatment options and make informed choices that align with their values and preferences. The remarkable histopathological heterogeneity of upper tract urothelial carcinoma (UTUC) and bladder presents a formidable challenge for clinicians and pathologists alike. This diversity in tumor morphology and behavior necessitates a nuanced approach to diagnosis, classification, and treatment, demanding expertise and meticulous attention to detail. Accurately diagnosing and classifying UTUC and bladder subtypes can be a daunting task, even for seasoned professionals. The subtle nuances that distinguish one subtype from another often require careful examination and interpretation of histopathological features. The morphological differences between certain subtypes, particularly the rarer variant subtypes, can be subtle and easily overlooked. For instance, distinguishing nested UTUC and bladder from benign mimics, such as nephrogenic metaplasia, requires careful assessment of cytological features and architectural patterns. The diagnosis of UTUC and bladder often relies on biopsy specimens obtained through ureteroscopy or percutaneous nephroscopy. These procedures may yield limited tissue samples, potentially hindering the accurate assessment of tumor heterogeneity. Even among experienced pathologists, there can be interobserver variability in the interpretation of histopathological features. This subjectivity can lead to discrepancies in diagnosis and classification, potentially impacting treatment decisions and patient outcomes. The heterogeneity of UTUC and bladder complicates treatment decisions, as there is no one-size-fits-all approach. The optimal treatment strategy must be tailored to the specific subtype, considering its aggressiveness, risk of recurrence, and potential response to therapy. Clinicians must carefully weigh the potential benefits of aggressive treatment against the associated risks and morbidities. For instance, while adjuvant chemotherapy may improve outcomes for patients with high-grade UTUC and bladder, it also carries the risk of significant side effects. The optimal treatment for variant subtypes, such as micropapillary and sarcomatoid UTUC and bladder, remains less well-defined due to their rarity and limited clinical trial data. Clinicians often rely on expert opinion and extrapolation from data on conventional urothelial carcinoma to guide treatment decisions. The advent of novel therapies, such as immunotherapy and targeted therapy, has expanded the treatment landscape for UTUC and bladder. However, the efficacy of these therapies may vary across different subtypes, requiring further research to optimize their use. Overcoming the challenges posed by histopathological heterogeneity in UTUC and bladder requires a multi-pronged approach, encompassing advancements in diagnostic techniques, refinement of treatment strategies, and ongoing research to deepen our understanding of this complex disease. The development of more sensitive and specific diagnostic tools, such as molecular profiling and immunohistochemical markers, can aid in the accurate classification of UTUC and bladder subtypes. Close collaboration between urologists, pathologists, oncologists, and radiologists is crucial for optimizing the diagnosis and treatment of UTUC and bladder. Multidisciplinary tumor boards can facilitate shared decision-making and ensure that patients receive individualized care. Participation in clinical trials is essential to evaluate the efficacy of new therapies and refine treatment strategies for different subtypes of UTUC and bladder.[13-18]

Intratubular spread, a hallmark of upper tract

urothelial carcinoma (UTUC) and bladder, involves the intricate process of cancer cell infiltration into the renal tubules. This retrograde spread, often observed in high-grade tumors, represents a complex interplay of cellular and microenvironmental factors that contribute to the aggressive nature of UTUC and bladder. While the exact mechanisms underlying intratubular spread remain an area of active investigation, several key factors have been implicated in this phenomenon. Cell adhesion, the intricate process that binds cells together to form tissues and organs, plays a crucial role in maintaining tissue integrity and preventing uncontrolled cell migration. In cancer, however, this delicate balance is often disrupted, as cancer cells acquire the ability to detach from the primary tumor and invade surrounding tissues. In UTUC and bladder, the loss of cell adhesion is a critical step in the process of intratubular spread. Cancer cells lose the expression of adhesion molecules, such as E-cadherin, that normally bind them together. This loss of adhesion allows the cancer cells to break free from the primary tumor mass and embark on their journey into the renal tubules. The disruption of cell adhesion is often driven by genetic alterations that affect the expression or function of adhesion molecules. For instance, mutations in the CDH1 gene, which encodes E-cadherin, are frequently observed in UTUC and bladder and other cancers. These mutations can lead to reduced expression or impaired function of E-cadherin, weakening the bonds that hold cells together and facilitating their detachment. Motility, the ability of cells to move and migrate, is essential for various physiological processes, such as wound healing and immune response. However, in cancer, increased motility can fuel the invasive and metastatic potential of tumor cells. In UTUC and bladder, cancer cells often acquire enhanced motility, enabling them to actively invade the renal tubules. This increased motility is driven by a complex network of signaling pathways that regulate cell movement, including the Rho GTPase family, focal adhesion kinase (FAK), and matrix metalloproteinases (MMPs). The Rho GTPase family, a group of signaling proteins that control the dynamics of the actin cytoskeleton, plays a central role in regulating cell motility. In UTUC and bladder, aberrant activation of Rho GTPases, such as RhoA and Rac1, can enhance cell motility and promote invasion. FAK, a non-receptor tyrosine kinase, is another key regulator of cell motility. It integrates signals from integrins, cell surface receptors that mediate cell adhesion to the extracellular matrix, and growth factor receptors, promoting cell migration and invasion. MMPs, a family of enzymes that degrade the extracellular matrix, also contribute to increased motility in UTUC and bladder. By breaking down the barriers that surround cells, MMPs create pathways for cancer cells to invade the renal tubules and other tissues. Chemotaxis, the directed movement of cells in response to chemical signals, plays a crucial role in guiding various physiological processes, such as immune cell recruitment and wound healing. However, in cancer, chemotaxis can also guide the migration and invasion of tumor cells. In UTUC and bladder, chemical signals released by the renal tubules may attract cancer cells, guiding their infiltration and contributing to intratubular spread. These chemotactic signals may include growth factors, cytokines, and chemokines, which bind to specific receptors on cancer cells and trigger intracellular signaling pathways that promote cell movement. The identification of specific chemotactic factors involved in intratubular spread could pave the way for novel therapeutic strategies aimed at disrupting this process. By blocking the signaling pathways or receptors involved in chemotaxis, it may be possible to inhibit the invasion of cancer cells into the renal tubules and reduce the risk of recurrence and metastasis. Pressure gradients within the urinary tract may also contribute to intratubular spread by facilitating the passive movement of cancer cells into the renal tubules. The pressure within the renal pelvis and ureters is normally higher than that within the renal tubules. This pressure difference may create a driving force that propels cancer cells, particularly those that have lost cell adhesion, into the renal tubules. While pressure

gradients may play a role in intratubular spread, they are likely not the sole determinant of this phenomenon. Active mechanisms, such as increased motility and chemotaxis, are also crucial for cancer cells to effectively invade and colonize the renal tubules.[19-22]

Intratubular spread, a distinctive histopathological feature characterized by the infiltration of cancer cells into the renal tubules, carries significant clinical implications for patients with upper tract urothelial carcinoma (UTUC) and bladder. Its presence often heralds a more aggressive disease course, posing challenges in treatment and impacting long-term outcomes. One of the most concerning clinical implications of intratubular spread is the heightened risk of local recurrence after surgery. Even with complete surgical removal of the primary tumor, microscopic cancer cells that have invaded the renal tubules may remain undetected and serve as a nidus for future tumor development. These lurking cancer cells can evade even the most meticulous surgical resection, potentially leading to the recurrence of UTUC and bladder within the renal pelvis, ureter, or even the bladder. The risk of recurrence is particularly elevated in patients with high-grade UTUC and bladder exhibiting extensive intratubular spread. The aggressive nature of these tumors, coupled with their ability to infiltrate deep into the renal parenchyma, makes complete eradication challenging, increasing the likelihood of recurrence and compromising long-term survival. The presence of intratubular spread serves as a prognostic indicator, signaling a more aggressive disease course and poorer overall survival outcomes. Patients with UTUC and bladder exhibiting intratubular spread generally have a worse prognosis compared to those without this feature, even after adjusting for other prognostic factors such as tumor stage and grade. The association between intratubular spread and poorer prognosis likely stems from the ability of cancer cells to invade beyond the confines of the primary tumor. This invasion into the renal tubules not only increases the risk of local recurrence but also raises the likelihood of distant metastasis, as cancer cells gain access to the lymphatic and vascular systems within the renal parenchyma. Intratubular spread poses significant challenges for the treatment of UTUC and bladder, as it necessitates strategies to eradicate cancer cells residing within the renal tubules. While radical nephroureterectomy (RNU) remains the cornerstone of treatment, the presence of intratubular spread may necessitate more extensive surgery or adjuvant therapy to achieve complete tumor eradication. In some cases, surgeons may opt for a more extensive resection of the kidney and ureter to encompass the areas affected by intratubular spread. This approach aims to minimize the risk of leaving behind residual cancer cells that could lead to recurrence. However, extended resection may also increase the risk of surgical complications and compromise renal function. Adjuvant therapy, such as chemotherapy or radiation therapy, may be considered to eliminate any residual cancer cells that may have evaded surgical resection. However, the optimal adjuvant therapy regimen for patients with intratubular spread remains an area of ongoing research. Novel therapies, such as immunotherapy and targeted therapy, are being investigated for their potential to improve outcomes for patients with UTUC and bladder, including those with intratubular spread. These therapies hold promise in targeting cancer cells specifically, while sparing healthy tissues, potentially reducing the risk of recurrence and improving survival. Microsatellite instability (MSI) is a molecular fingerprint of genomic instability, characterized by alterations in the length of repetitive DNA sequences known as microsatellites. These alterations, arising from defects in the DNA mismatch repair (MMR) system, represent a crucial aspect of tumor biology, with significant implications for prognosis, treatment response, and personalized medicine. Microsatellites, also known as short tandem repeats (STRs), are short, repetitive DNA sequences scattered throughout the genome. These sequences, typically consisting of 1-6 base pairs repeated multiple times, are highly polymorphic, meaning they vary in length among

individuals. Microsatellites play diverse roles in cellular processes, including DNA replication, gene regulation, and chromatin organization. However, their repetitive nature makes them susceptible to errors during DNA replication, potentially leading to insertions or deletions of repeat units. The DNA mismatch repair (MMR) system is a critical cellular surveillance mechanism that safeguards genomic integrity by correcting errors that occur during DNA replication. This intricate system, composed of several key proteins, including MLH1, MSH2, MSH6, and PMS2, acts as a molecular "spell-checker," identifying and repairing mismatched base pairs and insertion-deletion loops that arise during DNA replication. Microsatellite instability (MSI) arises from defects in the MMR system, leading to the accumulation of errors in microsatellite sequences. These errors manifest as alterations in the length of microsatellites, either expansions or contractions, compared to the corresponding sequences in normal cells. Inherited mutations in MMR genes, such as MLH1, MSH2, MSH6, and PMS2, predispose individuals to Lynch syndrome, a hereditary cancer syndrome associated with an increased risk of colorectal, endometrial, and other cancers. Acquired mutations in MMR genes can occur sporadically in tumor cells, leading to MSI in the absence of a hereditary predisposition. Epigenetic modifications, such as DNA methylation, can silence the expression of MMR genes, impairing their function and contributing to MSI. MSI is particularly prevalent in sporadic UTUC and bladder cases, those not associated with a hereditary predisposition. The prevalence of MSI in UTUC and bladder varies depending on the specific cohort and detection methods, but it is generally estimated to be around 20-30%. MSI is generally associated with a favorable prognosis in UTUC and bladder, as tumors with this feature tend to be less aggressive and less likely to metastasize. This improved prognosis may be attributed to the increased immunogenicity of MSI-high tumors, making them more susceptible to immune surveillance and attack. MSI has emerged as a predictive marker for response to immunotherapy, a type of cancer treatment that harnesses the power of the immune system to fight cancer. Patients with MSI-high tumors are more likely to benefit from immune checkpoint inhibitors, such as pembrolizumab and nivolumab, which unleash the anti-tumor activity of T cells. The MMR deficiency underlying MSI can be exploited therapeutically. PARP inhibitors, a class of drugs that target DNA repair pathways, have shown promising activity in MSI-high tumors. By inhibiting PARP, a key enzyme involved in DNA repair, these drugs can induce synthetic lethality in cancer cells with MMR deficiency, leading to their demise.[23-26]

4. Conclusion

This systematic review underscores the significant histopathological heterogeneity of UTUC and bladder, a critical factor influencing tumor behavior and patient outcomes. The presence of diverse subtypes, each with distinct features and prognostic implications, necessitates a nuanced approach to diagnosis and treatment. Integrating histopathological evaluation with molecular profiling can refine risk stratification and guide personalized treatment decisions. Further research is needed to unravel the complex interplay of these factors and develop targeted therapies for improved UTUC and bladder management.

5. References

1. Ogbue O, Haddad A, Almassi N, Lapinski J, Daw H. Overview of histologic variants of urothelial carcinoma: current trends and narrative review on treatment outcomes. Transl Androl Urol. 2022; 11(6).
2. D'Elia C, Trenti E, Krause P. Xpert® bladder cancer detection as a diagnostic tool in upper urinary tract urothelial carcinoma: preliminary results. Ther Adv Urol. 2022; 14.
3. Al Saidi I, Mohamedabugroon A, Sawalha A, Sultan I. Epidemiology of bladder cancer in the Arab World: 2019 Global Burden of Disease Data. Asian Pacific J Cancer Prev. 2022; 23(9): 2907-19.
4. Amin MB. Histological variants of urothelial

carcinoma: Diagnostic, therapeutic and prognostic implications. Mod Pathol. 2009; 22(Suppl 2).
5. Senduk SS, Rotty LW. Carcinoma of the bladder. J Biomed. 2013; 2(1).
6. Stewart GD, Bariol S V., Grigor KM, Tolley DA, McNeill SA. A comparison of the pathology of transitional cell carcinoma of the bladder and upper urinary tract. BJU Int. 2005; 95(6): 791-3.
7. Bettany-Saltikov J. How to do a systematic literature review in nursing: a step by-step guide. McGraw-Hill/Open University Press; 2018.
8. Giudici N, Bonne F, Blarer J, Minoli M, Krentel F, Seiler R. Characteristics of upper urinary tract urothelial carcinoma in the context of bladder cancer: a narrative review. Transl Androl Urol. 2021; 10(10): 4036-50.
9. Cosentino M, Palou J, Gaya JM, Breda A, Rodriguez-Faba O, Villavicencio-Mavrich H. Upper urinary tract urothelial cell carcinoma: Location as a predictive factor for concomitant bladder carcinoma. World J Urol. 2013; 31(1): 141-5.
10. Rink M, Robinson BD, Green DA. Impact of histological variants on clinical outcomes of patients with upper urinary tract urothelial carcinoma. J Urol. 2012; 188(2): 398-404.
11. Zamboni S, Foerster B, Abufaraj M. Incidence and survival outcomes in patients with upper urinary tract urothelial carcinoma diagnosed with variant histology and treated with nephroureterectomy. BJU Int. 2019; 124(5): 738-45.
12. Langner C, Hutterer G, Chromecki T, Rehak P, Zigeuner R. Patterns of invasion and histological growth as prognostic indicators in urothelial carcinoma of the upper urinary tract. Virchows Arch. 2006; 448(5): 604-11.
13. Rolim I, Henriques V, Rolim N. Clinicopathologic analysis of upper urinary tract carcinoma with variant histology. Virchows Arch. 2020; 477(1): 111-20.
14. Wasco MJ, Daignault S, Zhang Y. Urothelial carcinoma with divergent histologic differentiation (mixed histologic features) predicts the presence of locally advanced bladder cancer when detected at transurethral resection. Urology. 2007; 70(1): 69-74.
15. Shinagare AB, Ramaiya NH, Jagannathan JP, Fennessy FM, Taplin ME, Van Den Abbeele AD. Metastatic pattern of bladder cancer: Correlation with the characteristics of the primary tumor. Am J Roentgenol. 2011; 196(1): 117-22.
16. Xylinas E, Rink M, Robinson BD. Impact of histological variants on oncological outcomes of patients with urothelial carcinoma of the bladder treated with radical cystectomy. Eur J Cancer. 2013; 49(8): 1889-1897.
17. Kim MH, Yuk HD, Jeong CW, Kwak C, Kim HH, Ku JH. Estimated glomerular filtration rate as a prognostic factor in urothelial carcinoma of the upper urinary tract: a systematic review and meta-analysis. J Clin Med. 2021; 10(18).
18. Ciancio G, Tabbara MM, Martucci M, Gaynor JJ, Morsi M, Gonzalez J. Surgical management of upper urinary tract urothelial cell carcinoma with venous tumor thrombus: a liver transplant-based approach. J Clin Med. 2021; 10(24).
19. Park BH, Jeon SS. Endoscopic management of upper urinary tract urothelial carcinoma. Korean J Urol. 2013; 54(7): 426-32.
20. Catto JWF, Azzouzi AR, Rehman I. Promoter hypermethylation is associated with tumor location, stage, and subsequent progression in transitional cell carcinoma. J Clin Oncol. 2005; 23(13): 2903-10.
21. Lin W, Pan X, Zhang C, Ye B, Song J. Impact of age at diagnosis of bladder cancer on survival: a surveillance, epidemiology, and end results-based study 2004-2015. Cancer Control. 2023; 30.

22. Prakash S. Unsuspected primary renal urothelial carcinoma with squamous differentiation in a background of long standing renal calculi: a case report. IP Int J Med Paediatr Oncol. 2020; 4(1): 47-49.
23. Lillesand M, Kvikstad V, Gudlaugsson E. Abstract A025: Integrating genomic alterations and histopathological features for enhanced risk stratification in non-muscle invasive bladder cancer. Clin Cancer Res. 2024; 30(10_Supplement): A025-A025.
24. Sekine H. A study of dysplasia associated with bladder cancer -histopathological findings of bladder giant sections and related urinary cytology. Japanese J Urol. 1989; 80(4): 545-54.
25. Lausenmeyer EM, Braun K, Breyer J. Strong expression of cancertestis antigens CTAG1B and MAGEA3 is correlated with unfavorable histopathological features and MAGEA3 is associated with worse progression-free survival in urothelial bladder cancer. Urol Int. 2019; 102(1): 113-7.
26. Ekmekci S, Küçük Ü, Kaya Ö, Yörükoğlu K. The association between the histopathological features and microsatellite instability in young patients with urothelial carcinoma of the bladder. Rev Assoc Med Bras. 2021; 67(1): 64-70.