

Global Research Trends and Frontiers in Upper Tract Urothelial Carcinoma: A Comprehensive Visualization and Bibliometric Analysis

Jianfeng Ye*, Jinhao Wu*, Xuexue Hao*, Pengyu Wang, Zhunan Xu, Li Liu, Xia Li, Xiaoqiang Liu

Department of Urology, Tianjin Medical University General Hospital, Tianjin, People's Republic of China

*These authors contributed equally to this work

Correspondence: Xiaoqiang Liu; Xia Li, Department of Urology, Tianjin Medical University General Hospital, Tianjin, People's Republic of China, Tel +86 13820915038; +86 022 60362255, Email xiaoqiangliu1@163.com; jianzhixin5@126.com

Purpose: Upper tract urothelial carcinoma (UTUC) is a rare malignant tumor of the urinary tract. Understanding this complex condition requires insights from multiple disciplines, including urology, oncology, molecular biology, genetics, and immunology. The objective of this study was to identify research trends and emerging research hotspots in UTUC research by using bibliometric analysis.

Methods: UTUC publications were retrieved from the Web of Science Core Collection (WoSCC) on 8 December 2024 and analyzed with VOSviewer and CiteSpace to assess trends, collaborations, and research hotspots, with emphasis on the top 50 citation bursts.

Results: This study analyzed 3,226 publications on UTUC from 1998 to 2024, revealing a consistent upward trend in both annual publication output and citation frequency. The United States emerged as the leading country in terms of publication volume, total citations, and international collaboration intensity. Among research institutions, the Medical University of Vienna published the highest number of publications, while the University of Texas MD Anderson Cancer Center achieved the highest H-index. Meanwhile, Pierre and Marie Curie University led in average citations per publication. Shahrokh F. Shariat was identified as the most prolific author, excelling in both citation count and H-index. Urologic Oncology: Seminars and Original Investigations ranked highest in publication volume, whereas European Urology demonstrated the strongest academic impact. Keyword analysis indicated shifting research hotspots over time, with growing interest in kidney-sparing surgery, biomarker, neo/adjuvant therapies, and multicenter clinical trials, signaling potential future directions for UTUC research.

Conclusion: Our bibliometric analysis provides an overview of current UTUC research trends and emerging topics, which may help researchers identify areas for further investigation.

Keywords: bibliometric analysis, upper tract urothelial carcinoma, VOSviewer, CiteSpace, transitional cell carcinoma

Introduction

Urothelial carcinoma (UC) is the second most common urological malignancy in developed countries.¹ Upper tract urothelial carcinoma (UTUC), which arises in the renal pelvis and ureters, represents a rare subset of UC, accounting for only 5–10% of cases.² Among UTUC cases, tumors originating in the renal pelvis are approximately twice as common as those in the ureter. Multifocal tumors occur in 10–20% of cases.³ The highest incidence of UTUC is observed in individuals aged 70–90 years, with the disease being twice as prevalent in men as in women.⁴ The annual incidence of UTUC in Western countries is approximately 2 cases per 100,000 inhabitants.^{2,5} However, studies suggest that Asian populations may exhibit a higher incidence of UTUC, often presenting with more advanced disease and higher tumor grades compared to those in North America.⁶ Smoking and aristolochic acid are the most prominent environmental contributors.^{7–9} Lynch syndrome is a major genetic risk factor, and a history of bladder cancer (BC) further increases the risk of developing UTUC.^{10,11}

Patients classified as low-risk typically undergo kidney-sparing surgery, while those at high risk are treated with radical nephroureterectomy (RNU) combined with bladder cuff excision (BCE).² Neo/adjuvant and system treatment regimens for UTUC are often adapted from those used for BC due to the small number of cases. However, differences in anatomical location, histological characteristics, and the prevalence of key tumor genes highlight the need for further investigation into UTUC-specific therapies.^{3,12}

Bibliometrics applies mathematical and statistical methods to evaluate and analyze various aspects of textual information, aiming to uncover the processes of information dissemination and the nature and trends within a specific scientific discipline.¹³ The development of visualization tools, such as CiteSpace and VOSviewer, enables researchers to intuitively explore and visualize relationships based on publication, citation, and collaboration metrics derived from open-access databases.^{14,15} Bibliometric analyses often focus on English peer-reviewed articles and reviews, examining temporal trends, geographic and institutional output, and research hotspots to ensure consistency, reliability, and a comprehensive understanding of the field. Each year, hundreds of original articles and reviews related to UTUC are published. Nevertheless, to the best of our knowledge, a comprehensive bibliometric analysis of UTUC is still lacking. Addressing this gap is timely and essential, as our study applies advanced bibliometric techniques to map the current landscape of UTUC research and to provide a roadmap for future work.

Materials and Methods

Data Source and Search Strategy

The Web of Science (WoS) database was selected as the primary source for this study due to its extensive coverage of over 12,000 academic journals, offering the most comprehensive data for bibliometric analyses compared to other databases.¹³ Relevant publications published between 1998 and 2024 were retrieved on 8 December 2024 from the Web of Science Core Collection (WoSCC) using all available database versions. To ensure a robust and focused bibliometric analysis, the study included only articles and reviews published in English. The search strategy employed was: TS = (upper tract OR renal pelvis OR ureter) AND TS = (urothelial carcinoma OR transitional cell carcinoma) AND LA = (English) AND DT = (Article OR Review). Complete records, including references, were extracted from the retrieved publications and saved in plain text format for further analysis. Manual cleaning was conducted to merge author name variants and to standardize institutional and country names for consistency across records. As the study relied solely on publicly available bibliometric data, no ethical approval was required, in accordance with ethical research standards.

Bibliometric Analysis Tools and Visual Presentation

This study utilized Microsoft Excel 2021 (Microsoft, Seattle, WA, USA), VOSviewer (version 1.6.20), and CiteSpace (version 6.4.R1) to conduct the bibliometric analysis. Additionally, the online bibliometrics platform Bibliometric.com was employed to visualize international collaborations among countries and annual publication composition.

The number of publications, citations and keyword frequency were calculated using the VOSviewer software and ranked by Microsoft Excel. VOSviewer embedded clustering algorithm was employed to construct and visualize co-authorship, co-occurrence citation and co-citation networks, and time-overlay network.

CiteSpace was employed for dual-map journal overlays and identifying the 50 most prominent keywords and references based on citation bursts. The H-index of authors and institutions was obtained from the WoS database.

Results

Overview of Publication Status

This study analyzed 3,226 publications authored by 13,168 contributors from 76 countries and regions, affiliated with 3,088 academic institutions. These publications were disseminated across 435 journals and collectively cited 40,926 times by 5,041 publications published in other journals. [Figure 1](#) presents the chronological distribution of UTUC-related publications, showing a steady increase in the cumulative number of studies. Notably, the annual publication output doubled between 2011 and 2019. The relationship between cumulative publications and publication year was assessed

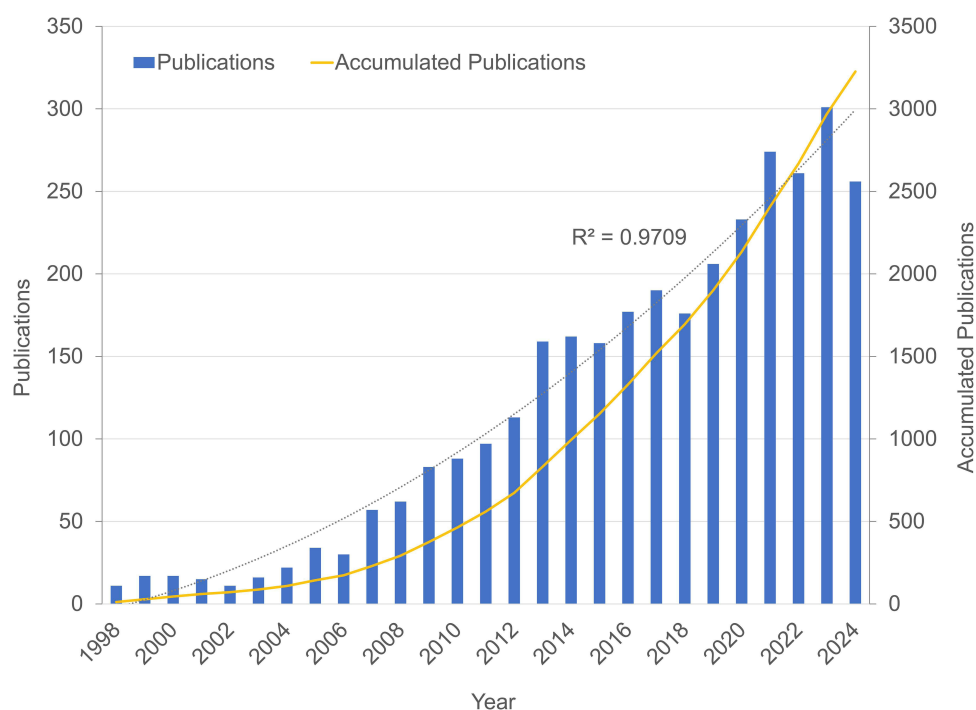


Figure 1 Annual Trends in Global Publications and Polynomial Fitting Curve for UTUC Research.

using an exponential growth function, which demonstrated a strong fit to the data ($R^2 = 0.9709$). This high correlation underscores the substantial advancement in UTUC research over the analyzed period.

Countries/ Regions

Researchers from 76 countries and regions have contributed to UTUC studies. The top ten countries with the highest number of publications and their corresponding citation metrics are summarized in [Table 1](#). Notably, the United States leads in both publication count and total citations, with an impressive average citation count of 34.71, underscoring its prominent scholarly output and research quality. This positions the United States as the global leader in UTUC research. Publications from European countries show notably high average citations per publication, reflecting their exceptional academic quality. Interestingly, China, as the sole developing country in the top ten, demonstrates a substantial volume of publications and an increasing proportion of publications year by year ([Figure 2B](#)). [Figure 2A](#), [C](#) and [D](#) highlights the United States as the central hub in the global UTUC research collaboration network. Active collaboration is observed

Table 1 Top 10 Most Productive Countries in UTUC Research

| Rank | Country | Counts | Total Citations | Average Citation per Publication | H-Index |
|------|-------------|--------|-----------------|----------------------------------|---------|
| 1 | USA | 1082 | 37,553 | 34.71 | 88 |
| 2 | China | 892 | 11,595 | 13.00 | 45 |
| 3 | Japan | 589 | 14,660 | 24.89 | 58 |
| 4 | Italy | 377 | 12,801 | 33.95 | 58 |
| 5 | France | 316 | 14,846 | 46.98 | 63 |
| 6 | Germany | 310 | 14,475 | 46.69 | 63 |
| 7 | Austria | 283 | 13,259 | 46.85 | 56 |
| 8 | Canada | 226 | 10,120 | 44.78 | 56 |
| 9 | UK | 174 | 9611 | 55.24 | 49 |
| 10 | South Korea | 157 | 2266 | 14.43 | 27 |

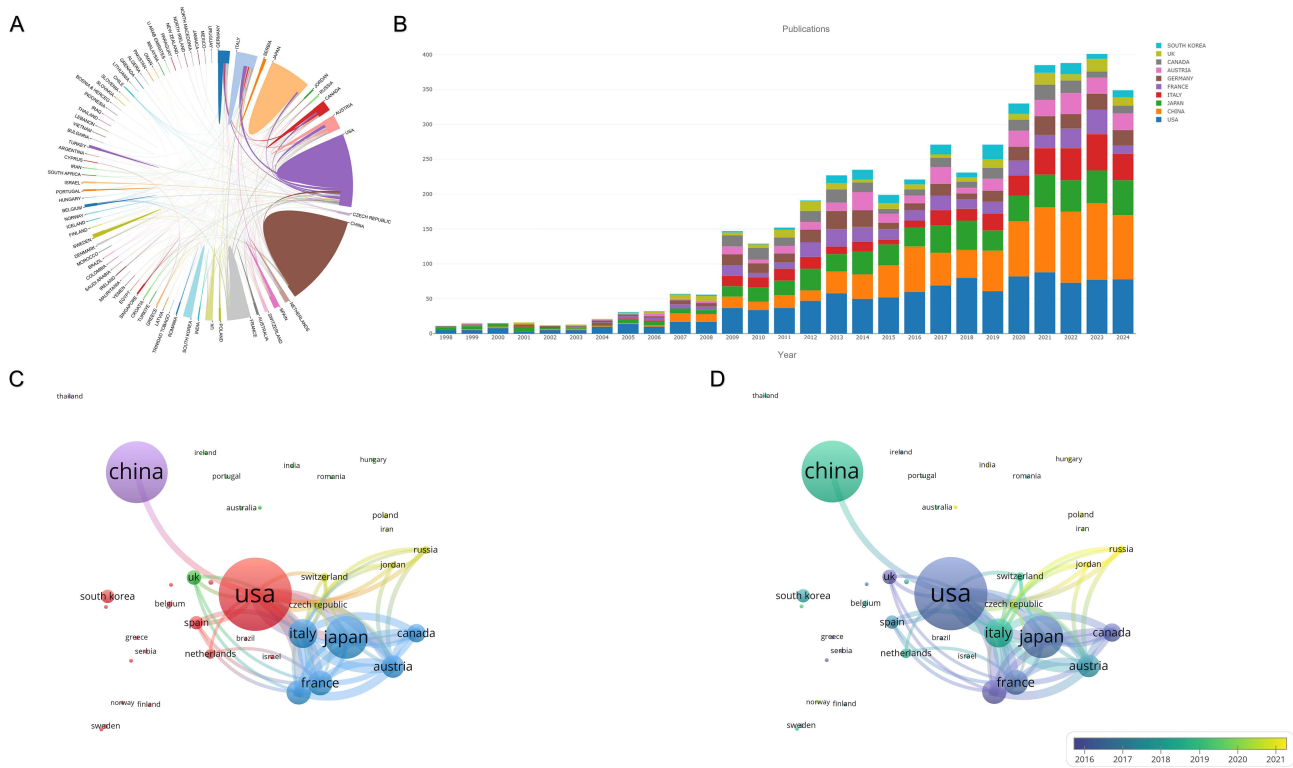


Figure 2 Graphical Representation of Countries' Co-Authorship Analysis. **(A)** Global collaborations in UTUC research. **(B)** Annual publication composition by the top 10 most productive countries/regions. Collaboration network clustering **(C)** and time-overlapping network **(D)** for countries/regions with at least five publications. The size of each node corresponds to the number of publications produced by the respective country. Connection lines between nodes indicate collaborative relationships, with the line width representing the total link strength. The relative distance between nodes reflects the level of cooperation between countries. Different colors denote distinct clusters identified through network analysis.

with countries such as China, Japan, France, Italy, Germany, Austria, and Canada, which represent key contributors to the field.

Institutions

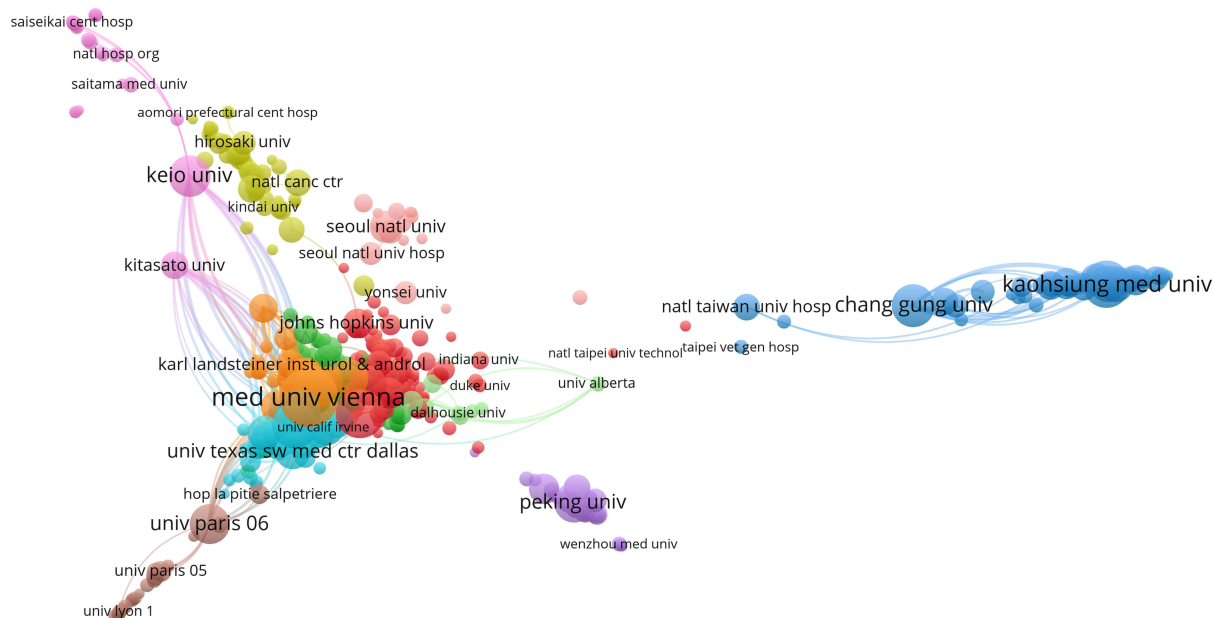
Table 2 highlights the ten research institutions contributing the most publications in UTUC research. The Medical University of Vienna ranks first in terms of publication count and total citations, reflecting its significant impact on UTUC research. In contrast, while the Pierre and Marie Curie University has a lower publication count, it boasts the highest average citation per publication, signifying exceptional academic quality.

Table 2 Top 10 Most Productive Institutions in UTUC Research

| Rank | Institutes | Country | Counts | Total Citations | Average Citation per Publication | H-Index |
|------|---|---------|--------|-----------------|----------------------------------|---------|
| 1 | Medical University of Vienna | Austria | 205 | 8043 | 39.23 | 46 |
| 2 | The University of Texas Md Anderson Cancer Center | USA | 136 | 7653 | 56.27 | 61 |
| 3 | Kaohsiung Medical University | China | 127 | 1902 | 14.98 | 25 |
| 4 | University of Montreal | Canada | 117 | 6377 | 54.50 | 48 |
| 5 | Vita-Salute San Raffaele University | Italy | 102 | 4718 | 46.25 | 39 |
| 6 | Chang Gung University | China | 101 | 1918 | 18.99 | 24 |
| 7 | Weill Cornell Medical College | USA | 101 | 3046 | 30.16 | 57 |
| 8 | Keio University | Japan | 95 | 4997 | 52.60 | 36 |
| 9 | Peking University | China | 89 | 1274 | 14.31 | 21 |
| 10 | Pierre And Marie Curie University | French | 87 | 5783 | 66.47 | 35 |

Figure 3 visualizes the collaboration network among research institutions. A total of 529 institutions with at least five publications formed 11 clusters. The largest cluster, led by the University of Texas MD Anderson Cancer Center, includes 120 institutions, predominantly from the United States. The collaboration network is primarily concentrated in

A



B

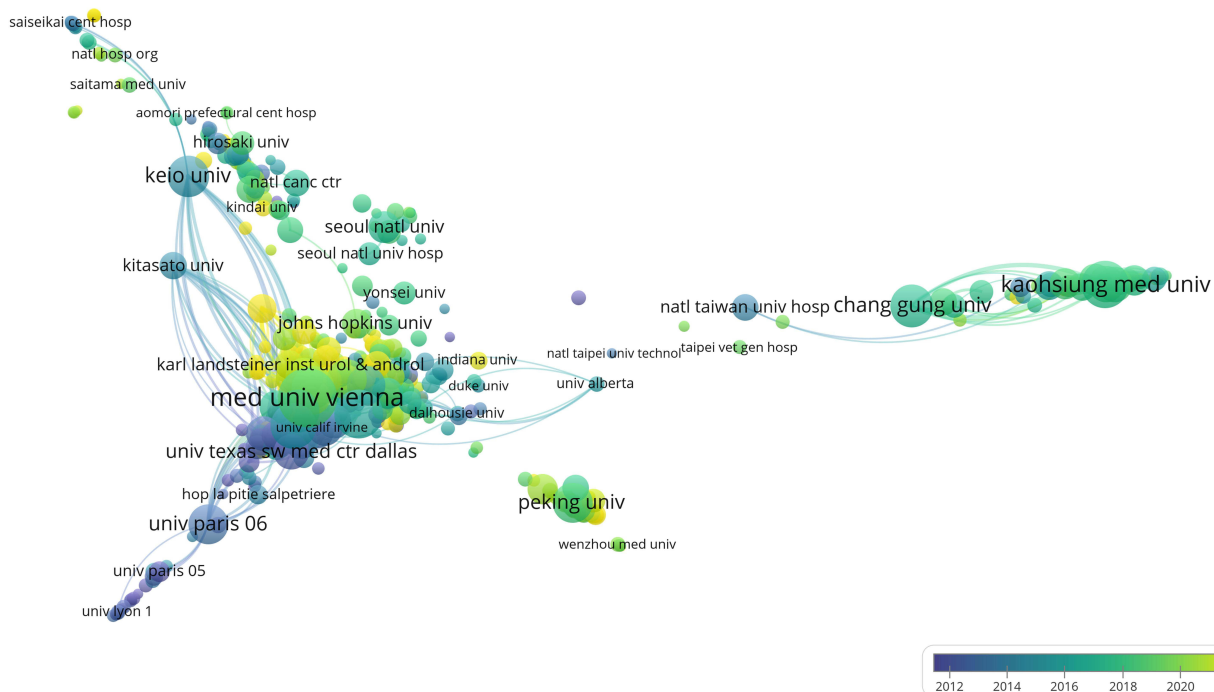


Figure 3 Graphical Representation of Institutional Co-Authorship Analysis. Collaboration network clustering (**A**) and time-overlapping network (**B**) for institutions with a minimum of five publications. The size of each node corresponds to the number of publications produced by the institution. Connection lines between nodes represent collaborative relationships, with line width indicating the total link strength. The relative distance between nodes reflects the level of cooperation. Different colors signify distinct clusters.

Table 3 Top 10 Most Productive Authors and Co-Cited Authors in UTUC Research

| Rank | Author | Counts | Total Citations | Average Citation per Publication | H-Index | Co-Cited Author | Total Citations |
|------|----------------------|--------|-----------------|----------------------------------|---------|---------------------|-----------------|
| 1 | Shahrokh F Shariat | 214 | 12,590 | 58.83 | 63 | Morgan Rouprêt | 2010 |
| 2 | Morgan Rouprêt | 137 | 7948 | 58.01 | 48 | Vitaly Margulis | 2010 |
| 3 | Vitaly Margulis | 111 | 4663 | 42.01 | 43 | Giovanni Lughezzani | 944 |
| 4 | Yair Lotan | 94 | 4923 | 52.37 | 41 | Thomas Seisen | 635 |
| 5 | Jay D Raman | 92 | 5492 | 59.70 | 46 | Evangelos N Xylinas | 633 |
| 6 | Wenjeng Wu | 84 | 1459 | 17.37 | 23 | Jay D Raman | 621 |
| 7 | Pierre I Karakiewicz | 77 | 4100 | 53.25 | 45 | Rebecca L Siegel | 608 |
| 8 | Eiji Kikuchi | 77 | 3989 | 51.81 | 36 | Marco Roscigno | 490 |
| 9 | Weiming Li | 72 | 1052 | 14.61 | 21 | Shahrokh F Shariat | 467 |
| 10 | Surena F Matin | 66 | 3424 | 51.88 | 29 | Michael Rink | 444 |

Europe and North America, characterized by high-intensity cooperation. However, collaboration in other regions remains limited, with a noticeable lack of cross-continental partnerships. These findings underscore the need to enhance global collaboration in UTUC research.

Authors

Table 3 highlights the ten authors with the highest publication output and the ten authors most frequently co-cited in the UTUC field. Among these, Shahrokh F Shariat, affiliated with the University of Vienna, stands out as the most prolific author, having published the largest number of works and received the highest number of citations. Figure 4A and B visualizes the collaborative network among authors. A total of 984 authors with five or more publications are grouped into 23 clusters. The network reveals a core of larger collaborative clusters alongside 14 relatively smaller ones. However, the analysis

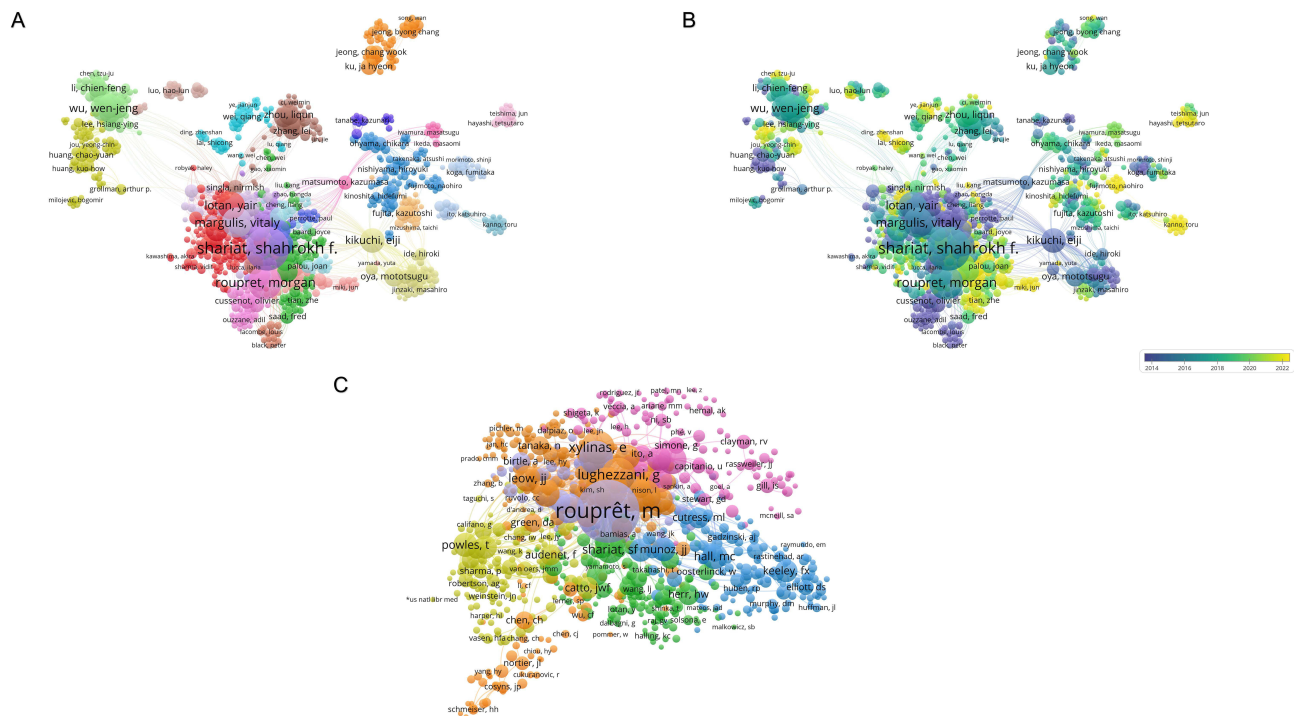


Figure 4 Graphical Representation of Authors' Co-Authorship Analysis and Authors' Co-Cited Analysis. Collaboration network clustering (A) and time-overlapping network (B) for authors with a minimum of five publications. (C) Network clustering for co-cited authors with a minimum of 20 citations. The size of each node corresponds to the number of publications or citations by the author. Connection lines between nodes represent collaborative relationships, with line width indicating the total link strength. The relative distance between nodes reflects the level of cooperation. Different colors signify distinct clusters.

indicates a lack of strong co-author relationships, suggesting that research contributions in this field are fragmented and regionally concentrated.

The author co-cited analysis sheds light on the connections between researchers with overlapping interests. The top ten most co-cited authors are also listed in [Table 3](#), while [Figure 4C](#) depicts the co-citation network.

Journals

[Table 4](#) presents a comprehensive summary of the top ten journals associated with UTUC research. Notably, six of these journals are based in the United States, while the remaining four are published in the United Kingdom, Switzerland, Japan, and the Netherlands. The impact factor (IF) of these journals range from 25.3 to 1.8. *European Urology* stands out with the highest IF of 25.3 and the largest number of total citations, amounting to an impressive 10,083. This underscores the substantial academic influence of *European Urology* within the UTUC field. Interestingly, despite publishing the highest number of publications, *Urologic Oncology: Seminars and Original Investigations* has a total of 2,921 citations and an IF of 2.4. This highlights a key issue in evaluating academic impact—the importance of considering both the quantity and the intrinsic quality of published works. Furthermore, nine of the top ten journals primarily focus on urology, while one is predominantly oriented toward oncology.

[Figure 5A](#) illustrates the interconnections among journals with related research interests. The analysis reveals a lack of significant collaborative interactions between these publications, suggesting that each journal contributes distinctive and original insights to the advancement of UTUC research, thereby exerting its own unique impact on the academic community. The dual-map overlay ([Figure 5B](#)) identifies two major publication centers connected by three prominent citation pathways. Journals in the Molecular/Biology/Immunology category primarily cite work published in the Molecular/Biology/Genetics category. Similarly, journals in the Medicine/Medical/Clinical category predominantly reference publications from the Molecular/Biology/Genetics and Health/Nursing/Medicine categories.

Reference

[Table 5](#) lists the ten most frequently cited references, each with over 200 citations. Among these, four are European Association of Urology (EAU) guidelines on UTUC. The most frequently cited references, titled “Outcomes of radical nephroureterectomy: a series from the Upper Tract Urothelial Carcinoma Collaboration”, has been cited 704 times. This study offers the strongest evidence supporting radical surgical treatment for UTUC. To analyze the interconnections among these co-cited references, a visual representation was employed ([Figure 6A](#)). While the figure provides an overview of their relationships, it reveals no significant clustering patterns, suggesting a diverse and wide-ranging body of literature.

[Figure 6B](#) highlights the top 50 references with the strongest citation bursts. Recent citation bursts have primarily focused on EAU guidelines, adjuvant and neoadjuvant therapies, molecular classification, and T-cell depletion in UTUC.

Table 4 Top 10 Journals in UTUC Research

| Rank | Source | Country | Counts | Total Citations | IF (2023) | JCR-c (2023) | H-Index |
|------|---|-------------|--------|-----------------|-----------|--------------|---------|
| 1 | Urologic Oncology: Seminars and Original Investigations | USA | 185 | 2955 | 2.4 | Q2 | 30 |
| 2 | BJU International | UK | 153 | 5948 | 3.7 | Q1 | 45 |
| 3 | World Journal of Urology | USA | 151 | 3336 | 2.8 | Q2 | 33 |
| 4 | Journal of Urology | USA | 145 | 7289 | 6.4 | Q1 | 47 |
| 5 | Urology | USA | 112 | 4110 | 2.1 | Q2 | 32 |
| 6 | Journal of Endourology | USA | 92 | 1645 | 2.9 | Q1 | 25 |
| 7 | Frontiers in Oncology | Switzerland | 89 | 411 | 3.5 | Q2 | 10 |
| 8 | Clinical Genitourinary Cancer | USA | 85 | 994 | 2.3 | Q2 | 17 |
| 9 | International Journal of Urology | Japan | 85 | 1539 | 1.8 | Q2 | 23 |
| 10 | European Urology | Netherlands | 79 | 10,083 | 25.3 | Q1 | 60 |

Table 5 Top 10 Co-Cited References in UTUC Research

| Rank | Source | Author | Year | Citations | Citations per Year | Doi |
|------|------------------------------------|---------------------|------|-----------|--------------------|-------------------------------|
| 1 | Cancer | Vitaly Margulis | 2009 | 704 | 44.00 | 10.1002/cncr.24135 |
| 2 | European Urology | Morgan Rouprêt | 2018 | 400 | 57.14 | 10.1016/j.eururo.2017.07.036 |
| 3 | European Urology | Morgan Rouprêt | 2021 | 387 | 96.75 | 10.1016/j.eururo.2020.05.042 |
| 4 | Journal of Urology | John J Munoz | 2000 | 332 | 13.28 | 10.1016/s0022-5347(05)67019-x |
| 5 | Urology | M Craig Hall | 1998 | 320 | 11.85 | 10.1016/s0090-4295(98)00295-7 |
| 6 | European Urology | Giovanni Lughezzani | 2012 | 282 | 21.69 | 10.1016/j.eururo.2012.02.030 |
| 7 | European Urology | Morgan Rouprêt | 2015 | 274 | 27.40 | 10.1016/j.eururo.2015.06.044 |
| 8 | European Urology | Morgan Rouprêt | 2013 | 247 | 20.58 | 10.1016/j.eururo.2013.03.032 |
| 9 | Ca-A Cancer Journal for Clinicians | Rebecca L Siegel | 2023 | 218 | 109.00 | 10.3322/caac.21387 |
| 10 | World journal of urology | Francesco Soria | 2017 | 210 | 26.25 | 10.1007/s00345-016-1928-x |

histopathological form of UTUC, demonstrated the strongest citation burst (strength: 43.45) and longest duration, spanning from 1998 to 2012. In recent years, keywords such as single arm, ureteroscopy, pembrolizumab, cisplatin ineligible patients, and multicenter have shown burst strengths exceeding 10, highlighting their dynamic influence as emerging research topics. These citation bursts underscore the evolving nature of UTUC research, reflecting the emergence of new themes and directions over time.

Discussion

In our study, bibliometric analysis was employed to examine the growth pattern of UTUC publications from 1998 to 2024. The growth of relevant research publications can be described in two phases according to their publication rate. Prior to 2006, the field experienced a slow growth phase, with fewer than 30 publications per year. The number of publications doubled to 57 in 2007 and reached a peak of 301 publications in 2023, suggesting that research on UTUC may have entered a phase of more rapid growth. This trend occurred concurrently with advancements in oncology research and an increasing recognition that UTUC, although less common, is a distinct type of cancer separate from BC.^{63,64} Various research institutions have recognized the research potential of UTUC, accompanied by enhanced funding and personnel support, contributing to progress in this field.

The top 10 countries contributed 78.3% of UTUC publications, with the United States and China leading. The United States played a central role in international collaborations, which may be related to its strong research investment, and expanding global cooperation could further advance UTUC research.

Among the top 10 research institutions in terms of publications, three were from China, three from the United States, and three from Europe. A comparison of average citations per publication revealed that institutions from China exhibited significantly lower citation rates compared to their counterparts. This finding highlights differences in citation impact, which may be related to factors such as research quality, language, or collaboration. Nonetheless, as a non-English-speaking developing country, China has made substantial progress in recent years, although its level of international collaboration remains limited, which may partly explain the relatively lower citation impact. The formation of the UTUC research consortium, led by the University of Texas MD Anderson Cancer Center, suggests that broader collaborations among institutions may help strengthen research competitiveness, particularly under financial or resource constraints.

Core journals are generally regarded as influential and tend to publish widely cited and foundational research. The academic impact of a journal is typically evaluated based on the number of publications, IF, H-index, and Journal Citation Reports (JCR) ranking. Urologic Oncology: Seminars and Original Investigations has the highest number of publications, while European Urology boasts the highest IF (IF 25.3) and H-index (H-index 60). Among the top ten journals, all are classified as either JCR Q1 or Q2. Notably, most of these journals are published in the United States, reflecting the country's substantial contribution to UTUC research. This underscores the importance of developing and establishing influential journals in other countries to strengthen their international academic presence.

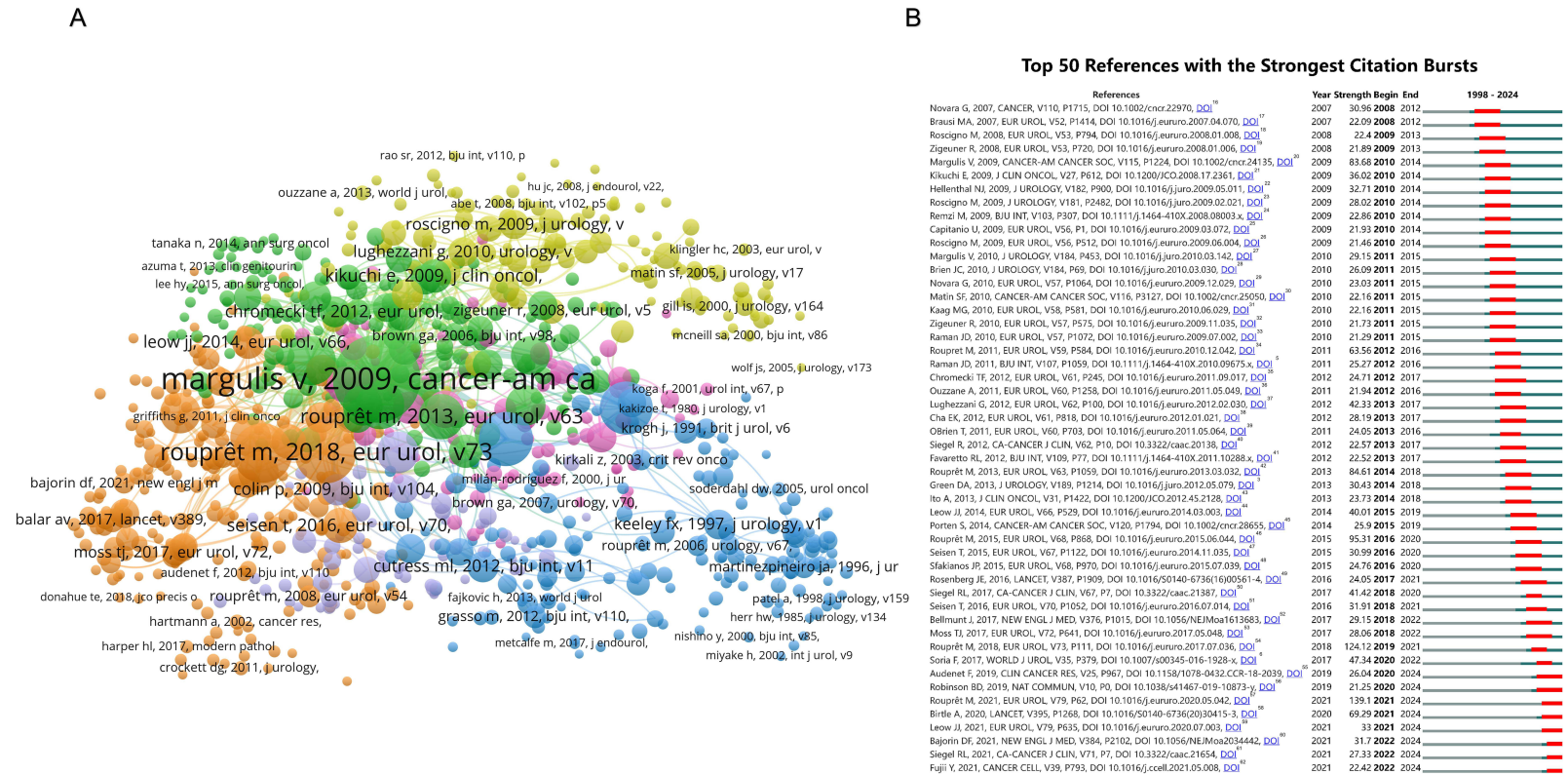


Figure 6 Graphical Representation of References' Co-Cited Analysis. **(A)** Network clustering for co-cited references with a minimum of 20 citations. The size of each node corresponds to the number of citations received by the reference. Connection lines between nodes represent collaborative relationships, with line width indicating total link strength. The relative distance between nodes reflects the strength of cooperation. Different colors signify distinct clusters. **(B)** Top 50 references with the strongest citation bursts.^{3,5,6,16–62}

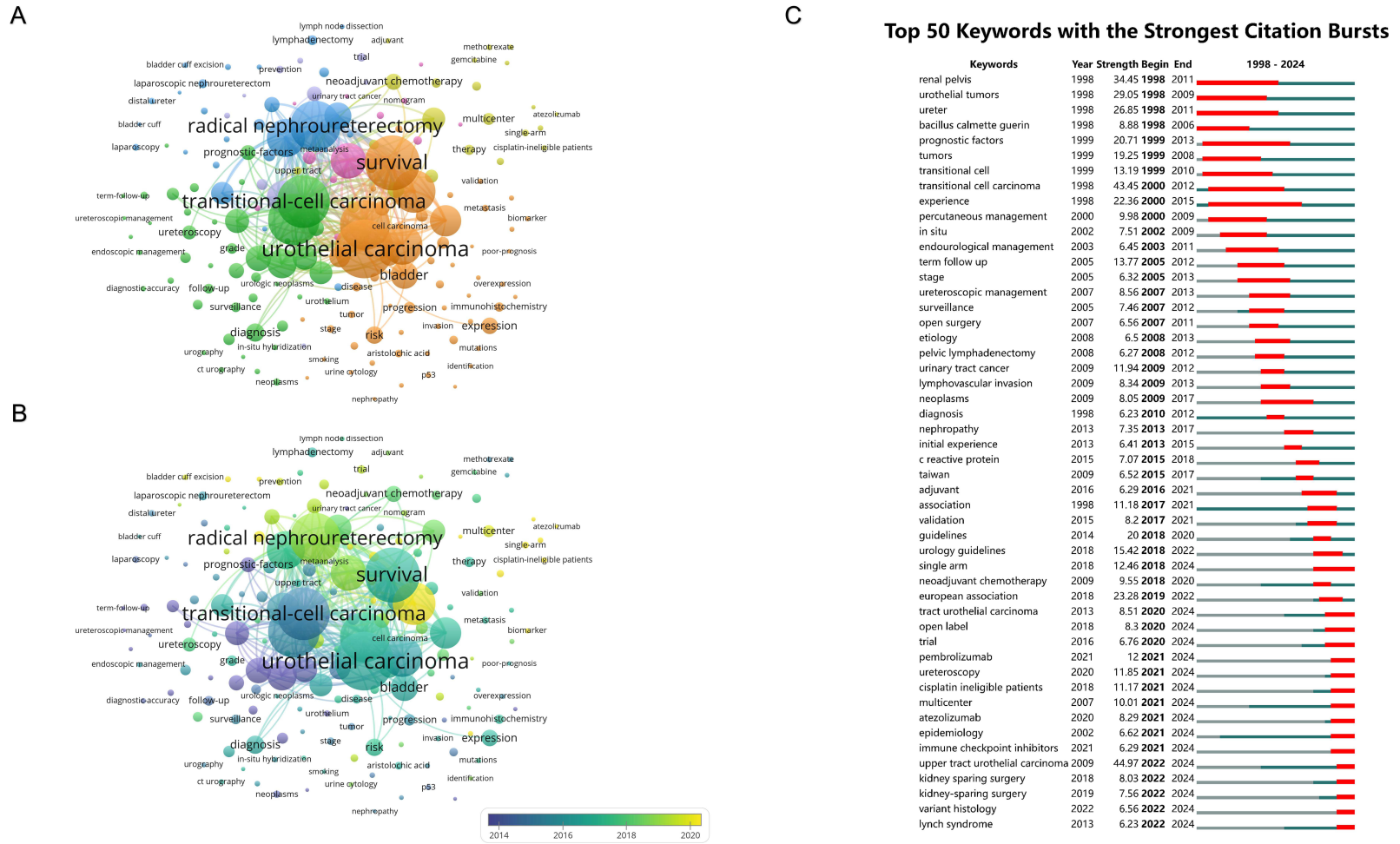


Figure 7 Graphical Representation of Keywords' Co-Occurrence Analysis. Network clustering (A) and time-overlapping network (B) for co-occurrence keywords with a minimum of 30 occurrences. The size of each node corresponds to the number of occurrences of the keyword. Connection lines between nodes represent collaborative relationships, with line width indicating total link strength. The relative distance between nodes reflects the strength of cooperation. Different colors signify distinct clusters. (C) Top 50 keywords with the strongest citation bursts.

Citation count serves as a key metric for evaluating the academic impact of a publication. Highly cited publications are often used as indicators to suggest research hotspots and emerging trends. In 1998, Hall et al⁶⁵ initially analyzed 252 UTUC patients and identified tumor stage and surgical procedure as key predictors of recurrence, while age and tumor stage impacted disease-specific survival. RNU provided effective local control in advanced cases. In 2009, Vitaly et al conducted a landmark study on the efficacy of RNU, which remains the most frequently cited research in the field of UTUC.²⁰ This study emphasized the critical role of RNU combined with BCE in UTUC management, while also drawing attention to the aggressive lymphatic behavior of UTUC and the necessity of templated LND and systemic therapies. The risk of LN metastasis increases with tumor stage and is closely linked to oncologic outcomes.^{20,66} Studies have shown that LND templates may have a greater impact on patient survival than the number of LNs excised whether LN status and T stage.^{67–70}

Keywords reflect the core subject of a study. By analyzing co-occurrences, researchers can identify high-frequency keywords, which can help indicate emerging research areas. Terms such as UC, transitional cell carcinoma and related terms are most common due to their prevalence as the primary pathology. The main treatments are RNU and chemotherapy, both well-documented, with their combination also assessed.⁵⁸ As in other oncological research, UTUC studies continue to focus on recurrence, progression, and disease outcomes.

CiteSpace includes a method called burst detection, which can be used to detect keywords or references that exhibit notable temporal changes.¹⁴ Researchers can use keywords and references with emerging characteristics to identify research hotspots. Kidney-sparing surgery and ureteroscopy have gained considerable attention in recent years. According to EAU and American Urological Association (AUA) guidelines, kidney-sparing surgery is recommended for patients with localized low-risk disease or those unsuitable for radical surgery.^{2,71} Various approaches to kidney-sparing surgery have shown survival outcomes that appear comparable to RNU in carefully selected patients.^{51,72,73} In 2022, a multicenter Phase 3 clinical trial evaluated chemical ablation in kidney-sparing surgery.⁷⁴ Following six weekly retrograde instillations of mitomycin-containing reverse thermal gel (UGN-101), 41 patients (58%) achieved complete response, with 23 of them (56%) remaining disease-free for at least one year. Kaplan-Meier analysis estimated 12-month durability at 82% (95% CI: 66–91). Chemical ablation has shown promise as an option for kidney-sparing therapy.

In 2022, a notable citation burst was observed for Lynch syndrome. UTUC ranks as the third most common malignancy in Lynch syndrome patients after colorectal and endometrial cancers.⁷⁵ Lynch syndrome is strongly linked to mismatch repair (MMR) gene alterations, with MMR-related mutations reported more frequently in UTUC than in BC.⁷⁶ Studies on UTUC molecular subtypes in Lynch syndrome show that MSH2 and MSH6 are the most common MMR mutations.⁷⁷ Additionally, an analysis of the Chinese UTUC population identified germline P/LP mutations in MSH2, BRCA2, BRCA1, and BRIP1 as significantly associated with increased UTUC risk.⁷⁸ MMR deficiency (dMMR) is a validated biomarker in various tumors to predict immunotherapy efficacy, with 7.2% of UTUC classified as dMMR.^{55,79–81} However, research by Brian et al found that reduced expression of MMR mRNA and proteins in non-Lynch UTUC was not associated with significant microsatellite instability (MSI) or elevated tumor mutation burden (TMB) compared to BC.⁵⁶ Interestingly, UTUC exhibits luminal-papillary and T-cell depleted characteristics, potentially explaining its relatively poor response to immune checkpoint inhibitors in clinical trials.^{49,56,82} Genetic testing, immunotherapy biomarkers, and clinical treatment decisions are closely associated. Further research is essential to explore the role of dMMR in immunotherapy for UTUC patients, with or without Lynch syndrome.

Previously, the molecular pathogenesis of UTUC was poorly understood, and no reliable biomarkers were available for diagnosis or molecular classification. Fuji et al conducted an integrated genetic study that classified UTUC into five subtypes based on mutations in TP53, MDM2, RAS, and FGFR3.⁶² These subtypes differed in gene expression, tumor location, histology, and clinical prognosis. Notably, FGFR3 alterations are more frequent in UTUC than in BC, indicating that FGFR3-targeted therapies may have a greater impact on UTUC.⁸³ The prospect of investigating the combination of FGFR3 inhibitors and programmed death-1/ ligand 1 (PD-1/ PD-L1) inhibitors as a targeted therapy for T-cell depleted UTUC is a potential avenue for future research, given the reported association of FGFR3 alterations with the T-cell depleted immune contexture of UTUC and encouraging outcomes of FGFR3 inhibitor treatment, Erdafitinib, for locally advanced or metastatic UC.^{56,84}

The POUT study, which filled the long-standing gap in evidence for adjuvant therapy after radical surgery in UTUC, also coincided with notable citation bursts in our bibliometric analysis, as illustrated in Figure 6B.⁵⁸ This phase 3, open-label, randomized controlled trial focused on UTUC patients with pT2-pT4, N (any) or positive (pT any, N1-3) M0. The results demonstrated a significant improvement in disease-free survival (DFS): 3-year DFS was 71% versus 50%, and 5-year DFS was 63% versus 46%. DFS benefits were also observed across different chemotherapy regimens. In the CheckMate 274 study, adjuvant Nivolumab improved DFS both in the intention-to-treat population (20.8 months vs 10.8 months) and in high-risk muscle-invasive UC patients who had undergone radical surgery (pT3, pT4a, or pN+) with PD-L1 expression levels $\geq 1\%$.⁶⁰ Despite the overall DFS benefit, the UTUC subgroup, often T-cell depleted, appeared to derive limited benefit, and its long-term effect requires further evaluation. These findings suggest the potential role of adjuvant therapies in improving DFS for muscle-invasive or locally advanced UTUC. However, further studies are needed to evaluate their impact on cancer specific survival (CSS) and overall survival (OS).

To date, only several retrospective studies have demonstrated neoadjuvant chemotherapy potential in achieving pathological downstaging and complete response at the time of RNU.^{30,85,86} A multicenter retrospective study reported that neoadjuvant chemotherapy was associated with better RFS, CSS, and OS in high-risk patients, though no clear benefit was observed in low-risk patients.⁸⁷ In Phase II clinical trials, pathological complete response rates ranging from 14% to 19% have been achieved.^{88,89} Conversely, a single arm phase II study evaluating pembrolizumab as a neoadjuvant therapy in 10 high-risk UTUC patients found no pathological response and reported one treatment-related fatality.⁹⁰ In summary, current evidence indicates that neoadjuvant chemotherapy may be a more reliable option than neoadjuvant immunotherapy for high-risk UTUC patients.

Antibody-drug conjugates (ADCs) are considered a novel therapeutic approach, combining the pharmacodynamic properties of small-molecule drugs with the targeted delivery capabilities of monoclonal antibodies.⁹¹ Several ADCs have been recommended as second-line treatment options for patients with metastatic or locally advanced UTUC.⁹²⁻⁹⁶ Enfortumab Vedotin and Disitamab Vedotin demonstrate promising median progression-free survival (PFS) and OS.^{92,96} Notably, Enfortumab Vedotin offers a treatment option for cisplatin-ineligible patients who have been previously treated with PD-1 or PD-L1 inhibitors.⁹³ Beyond monotherapy, significant progress has been achieved in combination therapies. For instance, the Phase III randomized multicenter EV302 study reported superior outcomes with the combination of Enfortumab Vedotin and Pembrolizumab compared to chemotherapy in untreated patients with locally advanced or metastatic UC.⁹⁷ Preliminary findings also highlight the potential of combining Disitamab Vedotin with Toripalimab or Sacituzumab Govitecan with Pembrolizumab.^{98,99} Given the substantial therapeutic promise of ADCs, ongoing clinical trials are exploring both dual ADC therapies and ADCs as part of neoadjuvant treatment regimens.^{100,101}

To our knowledge, a bibliometric analysis of UTUC research has not been previously conducted in detail; this study summarizes trends and research hotspots. However, this study has limitations. First, it includes only English articles and reviews indexed in WoSCC, potentially omitting relevant research and introducing language bias. Second, older studies may have more citations, partly because of longer publication history, while recent high-quality studies may be under-represented due to citation lag. Third, limitations in the search strategy may have introduced bias.

Conclusion

This bibliometric analysis highlights the most influential institutions, researchers, journals, and references in UTUC, providing insights into research advancements, emerging trends, and frontiers. It also identifies key knowledge gaps that warrant further investigation, guiding future research.

Abbreviations

UC, urothelial carcinoma; UTUC, upper tract urothelial carcinoma; BC, bladder cancer; RNU, radical nephroureterectomy; BCE, bladder cuff excision; WoS, Web of Science; WoSCC, Web of Science Core Collection; IF, impact factor; EAU, European Association of Urology; JCR, Journal Citation Reports; AUA, American Urological Association; MMR, mismatch repair; dMMR, MMR deficiency; MSI, microsatellite instability; TMB, tumor mutation burden; PD-1/ PD-L1,

programmed death-1/ ligand 1; DFS, disease-free survival; CSS, cancer specific survival; OS, overall survival; ADCs, antibody-drug conjugates.

Data Sharing Statement

The data in this study are publicly available and not of a confidential nature. Upon reasonable request, the data can be obtained from Xiaoqiang Liu.

Ethical Approval

Ethical approval and patient consent were not required, as all analyses were based solely on literature research.

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Disclosure

The authors declare that this research was conducted without any commercial or financial relationships that could be perceived as potential conflicts of interest.

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