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Perioperative Management of Upper Tract Urothelial Carcinoma: Current Evidence and Future Directions

Short Title: Perioperative Management of UTUC.

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Abstract

Background:

Upper tract urothelial carcinoma (UTUC) is a rare but aggressive malignancy characterized by high rates of muscle-invasive and non-organ-confined disease at diagnosis, substantial postoperative renal function decline, and frequent intravesical recurrence. These clinical features complicate the use of cisplatin-based chemotherapy and limit the development of robust, disease-specific evidence. Most perioperative recommendations remain extrapolated from bladder cancer, and considerable uncertainty persists regarding the optimal integration of chemotherapy, immunotherapy, and emerging biomarkers. This review aims to synthesize contemporary evidence on neoadjuvant and adjuvant systemic therapy in UTUC, identify persistent gaps in clinical practice, and outline future research priorities in the era of biomarker-driven treatment.

Summary:

Neoadjuvant platinum-based chemotherapy has been evaluated in prospective phase II studies, which suggest potential benefits in terms of pathological downstaging and survival, with manageable toxicity profiles. Observational and propensity-adjusted studies reinforce these benefits, particularly in responders, and real-world data confirm expanding adoption in advanced and node-positive disease. Neoadjuvant immunotherapy as monotherapy has shown limited activity, while recent data from the iNDUCT trial indicate that early chemo-immunotherapy combinations are feasible but have not yet met primary efficacy endpoints.

Findings from the POUT trial show a significant improvement in disease-free survival with adjuvant chemotherapy; however, overall survival data remain immature at the time of premature study closure. Adjuvant immunotherapy trials, including IMvigor010, CheckMate 274, and AMBASSADOR, have not shown a definitive benefit in UTUC subgroup analyses, a finding that may reflect limited statistical power. Persistent challenges include inaccurate preoperative staging, limited use of lymphadenectomy, uncertain management of variant histology and clinically node-positive disease, and the unresolved role of carboplatin. Emerging biomarkers such as circulating tumor DNA and urine tumor DNA show promise for refining risk stratification and minimal residual disease assessment, but remain investigational and require UTUC-specific prospective validation.

Key Messages:

Neoadjuvant platinum-based chemotherapy is gaining acceptance as a perioperative strategy in UTUC, supported by prospective phase II data demonstrating pathological downstaging and manageable safety profiles.

Neoadjuvant immunotherapy as monotherapy has demonstrated limited activity to date, whereas chemo-immunotherapy combinations remain under evaluation, with early feasibility but immature efficacy results.

Adjuvant chemotherapy, as shown in the POUT trial, significantly improves disease-free survival; however, overall survival benefit remains uncertain due to premature study closure and immature follow-up.

Evidence for adjuvant immunotherapy in UTUC remains inconclusive, as subgroup analyses from IMvigor010, CheckMate 274, and AMBASSADOR have not demonstrated clear benefit (likely influenced by limited statistical power) highlighting the need for UTUC-specific randomized trials.

Emerging biomarkers, including predictive models and circulating tumor DNA, may help refine perioperative treatment selection and guide future individualized strategies.

1. Introduction

Urothelial carcinoma (UC) represents the second most frequent malignancy of the urinary tract in developed countries, and upper tract urothelial carcinoma (UTUC) constitutes only 5-10% of all cases, with an annual incidence of around two per 100.000 habitants in Western populations [1]. The disease predominantly affects elderly men, and in contrast to bladder cancer, UTUC often presents at an advanced stage, with nearly two-thirds of patients harbouring muscle-invasive disease and approximately 9% showing metastases at diagnosis [2]. Despite curative surgery, intravesical recurrence occurs in almost one-third of patients, underscoring the need for optimized systemic and surveillance strategies [3].

These clinical features pose several therapeutic challenges. Many patients are diagnosed with advanced or node-positive tumours at surgery, and the decline in renal function after radical nephroureterectomy (RNU) frequently limits the use of cisplatin-based chemotherapy [4]. Together with the scarcity of randomized trials, these factors contribute to heterogeneous treatment practices and variable outcomes.

Despite growing interest in perioperative systemic therapy, UTUC still lacks robust, disease-specific and oncological evidence to guide clinical decisions. Most recommendations are extrapolated from bladder cancer, and uncertainty persists regarding the optimal use of chemotherapy, immunotherapy, and emerging biomarkers. This gap underscores the need for a comprehensive synthesis of current data and identification of future research priorities.

This review provides an updated overview of perioperative management in UTUC, focusing on current evidence, ongoing challenges, and future perspectives

2. Methods

A narrative review of the literature was conducted to summarize current evidence on perioperative systemic therapy for UTUC. The review was performed following a structured approach inspired by PRISMA recommendations to enhance transparency of the literature search and selection process. A comprehensive

search of PubMed, Embase, and ClinicalTrials.gov databases was conducted up to October 2025 using combinations of the following terms: "*upper tract urothelial carcinoma*", "*perioperative*", "*neoadjuvant*", "*adjuvant*", "*chemotherapy*", "*immunotherapy*", "*circulating tumor DNA*", and "*biomarkers*". Only articles published in English were considered.

After removal of duplicates, titles and abstracts were screened for relevance. Full texts of potentially eligible articles were assessed for inclusion. Priority was given to prospective clinical trials, meta-analyses, and international guideline documents. Retrospective studies and recent conference abstracts were included when they provided complementary or emerging data not yet available in full publications.

Studies not related to perioperative systemic treatment in UTUC, non-oncological studies, case reports, and articles with insufficient clinical relevance were excluded. Data extraction and synthesis were performed qualitatively, and no formal systematic review or meta-analysis was undertaken.

The literature search and study selection were performed independently by two authors. Any discrepancies regarding study eligibility were resolved through discussion and consensus.

The study identification, screening, and selection process is summarized in a PRISMA flow diagram (Figure 1).

3. Results

3.1. Rationale for Neoadjuvant Chemotherapy in Upper Tract Urothelial Carcinoma

The rationale for neoadjuvant chemotherapy (NAC) in UTUC is grounded in two complementary principles: the opportunity to deliver cisplatin-based therapy before the predictable decline in renal function following RNU, and the potential to eradicate micrometastatic disease at an earlier, more chemosensitive stage. To date, evidence supporting this strategy is primarily derived from two prospective phase II studies.

In the multicenter phase II trial by Margulis et al. (2020), patients with high-risk UTUC received four cycles of accelerated MVAC (aMVAC: methotrexate, vinblastine, doxorubicin, and cisplatin), with gemcitabine-carboplatin reserved for cisplatin-ineligible patients. Using a binomial design, the study predefined a pathologic complete response (pCR) rate of ≥18% as clinically meaningful. Among 29 evaluable patients treated with aMVAC, a pCR rate of 13.8% was observed, while more than 60% achieved pathological downstaging to ≤ypT1. Treatment was feasible and associated with acceptable toxicity, with grade 3-4 adverse events occurring in 23% of patients and no treatment-related deaths [5].

More recently, Coleman et al. (2023) reported the results of a prospective phase II trial evaluating a modified, split-dose gemcitabine–cisplatin regimen designed to improve tolerability (gemcitabine 1.000 mg/m^2 and cisplatin 35 mg/m^2 on days 1 and 8 of a 21-day cycle, for four cycles). Using a Simon two-stage design, a pathological response rate (<ypT2N0) of ≥60% was defined as promising. Among 57 treated patients, 63% achieved <ypT2N0 and 19% achieved pCR, meeting the predefined efficacy threshold. With a median follow-up of 3.1 years, 2- and 5-year progression-free survival (PFS) rates were 89% and 72%, respectively, while overall survival (OS) rates were 93% and 79% [6].

These studies confirm that NAC is feasible and tolerable in carefully selected patients with UTUC and demonstrate that pathological response (particularly complete or near-complete downstaging) is strongly associated with favorable long-term outcomes (Table 1).

3.1.1 Evolving Adoption of Neoadjuvant Chemotherapy in UTUC

Although NAC remains underutilized overall, population-based studies demonstrate a clear and progressive increase in its use over time in patients with high-risk UTUC, reflecting evolving clinical practice and growing acceptance of perioperative systemic therapy.

In 2021, Hamaya et al. reported temporal trends in NAC utilization using a nationwide Japanese cohort of patients with high-risk UTUC treated with RNU. NAC use increased markedly across successive periods, rising from 19% in 2006-2010 to 58% in 2011-2015, and further to 79% in 2016-2020 ($p<0.01$ for both comparisons). This study provided early evidence of a rapid shift toward preoperative systemic therapy, particularly within high-volume and specialized centers [7].

More recently, Xu et al. (2024) analyzed data from the U.S. National Cancer Database, including 6.645 patients with UTUC treated between 2004 and 2019. Although the overall rate of NAC administration remained low (3.1%), utilization steadily increased over time, peaking at 8.8% in 2016. Importantly, receipt of

NAC was independently associated with treatment at academic centers (odds ratio (OR) 2.02, p<0.001), as well as with advanced clinical stage and nodal involvement, highlighting both increasing adoption and persistent disparities in access to perioperative chemotherapy [8].
These population-based data from distinct healthcare systems consistently demonstrate a gradual but sustained increase in NAC use for UTUC, particularly in patients with high-risk disease and those treated at academic institutions. While absolute utilization rates remain modest, these trends underscore a growing recognition of the potential advantages of delivering systemic therapy in the neoadjuvant setting and further emphasize the need for prospective studies to define its optimal role.

3.1.2 Real-World Evidence Supporting a Survival Benefit of Neoadjuvant Chemotherapy in UTUC: Data Derived from Observational Studies

Beyond prospective phase II trials, a growing body of observational evidence has explored the oncologic impact of NAC in patients with high-risk UTUC. Given the rarity of the disease and the absence of completed randomized phase III trials in the neoadjuvant setting, these real-world analyses (many of which apply modern causal inference techniques) provide important insights into the effectiveness of NAC in routine clinical practice.
Beyond documenting the increasing adoption of NAC in Japan, the same analysis by Hamaya et al. (2021), also provides some of the most robust comparative evidence regarding its oncologic impact. Using inverse probability of treatment weighting (IPTW) to balance baseline clinicopathologic characteristics between treatment groups, NAC was associated with significant improvements across multiple survival endpoints. After adjustment, NAC was associated with superior metastasis-free survival (MFS) (Hazard ratio (HR) 0.61, 95% CI 0.42-0.90, p=0.013), cancer-specific survival (CSS) (HR 0.50, 95% CI 0.31-0.80, p=0.004), and OS (HR 0.59, 95% CI 0.39-0.88, p=0.010), corresponding to an approximate 40-50% relative reduction in mortality risk compared with surgery alone [7].
Similar findings were observed in a large propensity score–based analysis by Chen et al., which compared NAC with upfront surgery alone in a retrospective UTUC cohort. After adjustment for demographic, clinical, and tumor-related variables, NAC remained independently associated with improved OS (adjusted HR 0.62, 95% CI 0.45-0.86) and CSS (adjusted HR 0.58, 95% CI 0.40-0.85). Notably, the magnitude of benefit closely mirrored that reported by Hamaya et al., reinforcing the reproducibility of the survival signal across different populations, healthcare systems, and analytical approaches [9].
Earlier institutional series have also supported the biological activity of NAC in UTUC. In a two-center retrospective study, Meng et al. (2019) evaluated cisplatin-based NAC in patients with high-grade UTUC and reported high response rates, with 80% achieving pathological downstaging (<pT2N0) and only 20% exhibiting ≥pT2 disease at final pathology compared with 64% among patients treated with upfront surgery (p=0.001). NAC-treated patients demonstrated longer PFS and OS, with no cases of disease progression during neoadjuvant therapy or compromise of definitive surgical management [10].
Population-based data from East Asia have yielded more heterogeneous results. In a nationwide Korean cohort study, Tae et al. (2022) compared NAC and adjuvant chemotherapy (AC) using propensity score matching. In this analysis of over 8.700 patients, no statistically significant difference in OS was observed between NAC and AC after matching (HR 0.83, 95%; CI 0.49-1.40, p=0.48) [11]. These findings underscore the influence of patient selection, disease stage distribution, and treatment heterogeneity in large administrative datasets, and highlight the challenges of isolating treatment effects in unselected national cohorts.
More recently, the ROBUUST 2.0 international registry has provided contemporary multicenter real-world evidence focusing on advanced disease. In this cohort of nearly 2.000 patients, NAC was preferentially administered to individuals with biologically aggressive features, including cT ≥ 3 tumors and clinically node-positive disease. On multivariable analysis, NAC was independently associated with improved CSS in patients with cT ≥ 3 disease (HR 0.44, 95% CI 0.20-0.96, p=0.04), and with improved CSS (HR 0.50, 95% CI 0.26-0.94, p=0.03) and OS (HR 0.53; 95% CI 0.31-0.91; p=0.02) in clinically node-positive patients. No significant increase in perioperative morbidity was observed, supporting the feasibility of NAC even in higher-risk populations [12].
These observational studies consistently suggest that NAC is associated with clinically meaningful survival benefits in selected patients with high-risk UTUC. While residual confounding inherent to non-randomized analyses cannot be fully excluded, the convergence of findings across independent cohorts, healthcare

systems, and analytical methodologies strengthens the biological plausibility of a true treatment effect and supports the relevance of NAC in contemporary clinical practice.
The key findings from these observational studies are summarized in Table 2.

3.1.3. Pathological Response as a Surrogate Marker of Long-Term Survival After Neoadjuvant Chemotherapy in UTUC

Across observational and multicenter datasets, a consistent and clinically meaningful prognostic gradient has emerged in UTUC patients treated with NAC, whereby survival outcomes are markedly superior among those achieving a pathological response--particularly complete response--compared with non-responders. Meng et al. (2019) provided early evidence of this response-dependent benefit in a two-center cohort of patients receiving NAC prior to radical nephroureterectomy. In this series, NAC achieved substantial pathological downstaging, with approximately 80% of patients attaining <pT2N0 disease. When outcomes were analysed according to response status, responders demonstrated superior oncologic outcomes compared with non-responders and patients treated with upfront surgery, with estimated 3-year PFS rates of approximately 70% versus 45%, respectively. A similar gradient was observed for OS, with 3-year OS probabilities exceeding 75% among responders compared with approximately 50% in non-responders, although statistical significance was limited by the small sample size and low event rate [10].
As previously mentioned, this response-dependent survival signal was also observed the large, population-based analysis by Xu et al. (2024) [8]. In this nationally representative cohort, pCR rates following NAC were modest (approximately 5%); however, the prognostic impact of response was striking. Any pathological response—defined as ≤pT1N0/X—was independently associated with a profound improvement in OS, with an adjusted HR of 0.18 (95% CI 0.12–0.27), corresponding to an approximately 80% relative reduction in mortality risk compared with non-responders. In probability terms, responders demonstrated markedly higher 5-year OS estimates (>80%) compared with non-responders (<55%), underscoring that survival benefit was largely confined to patients achieving tumour response.
More recently, Yu et al. (2025) provided robust confirmation of this concept in a large multi-institutional consortium. Patients achieving ≤ypT1N0 after NAC exhibited significantly superior long-term outcomes, with 5-year OS rates of 82% compared with 60% in non-responders and 5-year PFS rates of approximately 70% versus 45%, respectively. After multivariable adjustment, pathological responders retained a significantly reduced risk of death (adjusted HR for OS ~0.45, 95% CI 0.30–0.68) and disease progression (adjusted HR for PFS ~0.50, 95% CI 0.34–0.74). Median OS and PFS were not reached among responders, whereas both endpoints were substantially shorter in non-responders. Importantly, these associations were consistent in analyses restricted to cisplatin-treated patients, reinforcing pathological response as a robust surrogate of long-term benefit [13].
Complementary evidence is provided by the multicenter Taiwanese cohort reported by Chou et al. (2025), in which propensity score overlap weighting was applied and outcomes were stratified according to NAC response status, revealing a marked prognostic divergence. NAC non-responders experienced significantly worse outcomes than patients treated with adjuvant chemotherapy, with substantially inferior OS (HR 3.33, 95% CI 1.83-6.08; p<0.001), CSS (HR 2.97, 95% CI 1.50-5.87; p=0.002), and recurrence-free survival (RFS; HR 3.58, 95% CI 1.89-6.80; p<0.001). In contrast, patients who achieved a pathological response to NAC demonstrated survival outcomes comparable to those receiving adjuvant chemotherapy, with no significant differences in OS (HR 0.79, 95% CI 0.34-1.83), CSS (HR 0.50, 95% CI 0.16-1.61), or RFS (HR 1.57, 95% CI 0.95-2.58) [14].
Overall, the survival benefit of NAC is greatest among patients achieving pathological response, particularly ≤ypT1N0 or pathologic complete response, which consistently serve as robust surrogates of long-term survival in UTUC.

3.1.4 Pooled Evidence Supporting the Oncologic Impact of Neoadjuvant Chemotherapy in UTUC: Data Derived from Meta-Analyses

Multiple systematic reviews and meta-analyses have pooled the available evidence to better estimate the oncologic impact of NAC prior to RNU in UTUC, and their key findings are summarized in Table 3. Across these syntheses, the direction of effect is broadly consistent, demonstrating higher rates of pathological response and signals of improved survival outcomes with NAC. Interpretation, however, is tempered by substantial clinical and methodological heterogeneity, including variability in definitions of “high-risk”

disease; inclusion of locally advanced and/or node-positive tumours; mixed cisplatin- and carboplatin-based regimens; non-uniform pathological endpoints (pCR versus downstaging); inconsistent use and extent of lymphadenectomy; variability in pathological assessment; residual confounding inherent to non-randomized designs; overlapping institutional cohorts; and evidence of publication bias in selected comparisons.

A more methodologically explicit synthesis was provided by Leow et al. (2020). Despite acknowledging heterogeneity in response definitions and recurrence endpoints, this meta-analysis demonstrated a significant survival advantage for NAC compared with upfront surgery, with pooled HR of 0.44 for OS (OS; 95% CI 0.32-0.61) and 0.38 for CSS (95% CI 0.24-0.61). In addition, Leow et al. reinforced the biological activity of NAC, reporting pooled rates of pCR of 11% (95% CI 7-15%), major pathological response (≤ypT1N0M0) of 43% (95% CI 33-53%), and pathological downstaging of 33% (95% CI 14-52%) [15].

Subsequently, Oswald et al. (2022) restricted their analysis to comparative studies and reported consistent improvements in both pathological and survival outcomes. Using adjusted time-to-event estimates, NAC was associated with improved OS (IPTW-adjusted HR 0.51; 95% CI 0.40-0.66) and cancer- or disease-specific survival (IPTW-adjusted HR 0.44; 95% CI 0.32-0.61). A favorable association was also observed for PFS (HR 0.42; 95% CI 0.19-0.91), supporting a consistent benefit across clinically relevant endpoints [16].

The most recent and largest pooled analysis by Deb et al. (2024) further consolidated the pathological impact of NAC in UTUC by synthesizing data from more than 14.000 patients. In this comprehensive meta-analysis, treatment effects were primarily reported as ORs for pathological endpoints. Compared with upfront surgery, NAC was associated with a markedly higher likelihood of achieving pCR (OR 4.76; 95% CI 3.20-7.08) and significantly increased odds of pathological downstaging to ≤pT1 disease (OR 3.58; 95% CI 2.56-5.01). Conversely, NAC significantly reduced the likelihood of presenting with advanced pathological stage (≥pT3) at final pathology (OR 0.44; 95% CI 0.34-0.56), indicating a consistent shift toward more favourable surgical pathology [17]. Although survival outcomes were not uniformly pooled as time-to-event hazard ratios across all included studies, the direction and magnitude of these effect estimates strongly support a robust association between NAC and improved pathological disease control (an endpoint repeatedly linked to long-term oncologic benefit in UTUC).

Overall, pooled evidence from meta-analyses supports a reproducible association between NAC and improved pathological response in UTUC, with several syntheses also suggesting favorable survival outcomes. Nonetheless, the certainty of pooled survival estimates remains limited by retrospective study designs, heterogeneity in patient populations and treatment regimens, and residual confounding, underscoring the need for dedicated prospective randomized trials.

3.1.5 The Timing of Chemotherapy in UTUC Remains an Unmet Need: What Is the Optimal Time?

While the role of perioperative chemotherapy in high-risk UTUC is increasingly established, the optimal timing of its delivery remains unclear. This question is being prospectively addressed by the ongoing phase II URANUS trial (NCT02969083), which randomizes patients with cT2-pT4, cN0-1, M0 disease to receive either neoadjuvant platinum-based chemotherapy followed by RNU or upfront surgery followed by AC. By restricting enrollment exclusively to upper-tract tumors and applying stringent staging and eligibility criteria, URANUS is uniquely positioned to generate comparative data on the sequencing of perioperative systemic therapy and to help refine treatment algorithms in UTUC once mature results become available [18].

While awaiting the results of URANUS, complementary evidence has emerged from both decision-analytic modeling and contemporary real-world comparative studies. A Markov-based microsimulation comparing RNU alone, NAC, and AC in 100.000 simulated patients suggested a net clinical advantage for preoperative treatment. NAC was associated with longer median OS (123 months) compared with AC (111 months) and surgery alone (96 months), as well as higher quality-adjusted life expectancy (7.50 vs. 7.23 and 6.79 years, respectively). Although treatment-related toxicity was more frequent with NAC, completion rates were substantially higher than with postoperative chemotherapy (83.3% vs. 40%), underscoring the practical challenges of delivering systemic therapy after RNU [19].

In addition to its previously discussed findings, a multicenter Taiwanese real-world cohort study published in 2025 provided further insight by directly comparing NAC and AC using propensity score overlap weighting, a causal inference approach designed to emphasize patients with comparable probabilities of receiving either strategy. Among 249 patients with high-risk UTUC, NAC was associated with more favorable pathological characteristics at surgery, including a lower rate of advanced pathological stage (≤pT2 in 56%

vs. 38%), reduced lymph node involvement (18% vs. 32%), and lower prevalence of lymphovascular invasion (29% vs. 47%) compared with AC. After weighting, no statistically significant differences were observed between NAC and AC in OS, CSS, or RFS. However, treatment response emerged as a key determinant of outcome: NAC nonresponders experienced significantly worse overall and CSS than patients treated with AC, whereas NAC responders achieved survival outcomes comparable to the adjuvant cohort. These findings highlight both the potential benefit of earlier systemic therapy and the marked heterogeneity of response, reinforcing the need for improved patient selection and prospective validation [14].

3.2 Neoadjuvant Immunotherapy Monotherapy in UTUC: Limited Efficacy

PURE-02 represents, to date, the only prospective evaluation of neoadjuvant immunotherapy in UTUC. In this feasibility study, ten patients with localized, high-risk UTUC received single-agent pembrolizumab prior to RNU. Although 90% of patients completed the planned neoadjuvant treatment, antitumor activity was limited. Only one patient achieved a clinical complete response and declined surgery, while a favorable pathological response (ypT1N0) was observed in just 14.3% of patients undergoing surgery, corresponding to a tumor that was clinically non-invasive at baseline staging. Two patients (20%) experienced disease progression during neoadjuvant treatment and required subsequent chemotherapy. From a safety standpoint, one treatment-related death occurred due to severe immune-mediated toxicity, including myocarditis, myasthenia gravis, hepatitis, and myositis, underscoring the potential risks of this approach [20]. These findings indicate that pembrolizumab as single-agent neoadjuvant therapy in high-risk UTUC does not appear to be sufficiently effective and highlight both the biological uncertainty and the practical limitations associated with neoadjuvant immunotherapy in this setting.

3.3 Emerging Evidence from Neoadjuvant Chemo-Immunotherapy Combination Trials

The neoadjuvant chemo-immunotherapy strategy in UTUC has been primarily explored in the iNDUCT trial [21], a prospective, single-arm study designed to assess the feasibility and biological activity of combining platinum-based chemotherapy with immune checkpoint inhibition prior to RNU. Patients were stratified into two predefined cohorts according to baseline renal function. Those with an estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73 m^2 received gemcitabine plus cisplatin in combination with durvalumab, whereas patients with an eGFR between 40 and <60 mL/min/1.73 m^2 were treated with gemcitabine plus carboplatin combined with durvalumab. In both cohorts, durvalumab was administered every three weeks concomitantly with chemotherapy for four neoadjuvant cycles prior to surgery.

Updated results published in 2025 provided the first prospective efficacy data for this approach in UTUC. Among 49 evaluable patients, pCR rates were 13% in the cisplatin-based cohort and 5% in the carboplatin-based cohort. Tumor downstaging to ≤ypT1 was achieved in 50% and 42% of patients, respectively, indicating biological activity of the combined regimen despite not meeting the predefined pCR targets (≥20% in the cisplatin cohort and ≥10% in the carboplatin cohort). These findings support the capacity of neoadjuvant chemo-immunotherapy to induce meaningful pathological responses in a substantial proportion of patients [22].

From a safety standpoint, the regimen demonstrated an acceptable and manageable toxicity profile. No grade 5 adverse events and no grade 3-4 immune-related toxicities attributable to durvalumab were reported. Grade 3-4 adverse events were predominantly chemotherapy-related hematologic toxicities, including neutropenia (10%), anemia (8%), and thrombocytopenia (4%). Importantly, treatment-related toxicity did not compromise surgical feasibility, and nearly all patients successfully proceeded to planned RNU without delay or cancellation.

Although the primary efficacy endpoints were not met, iNDUCT established the feasibility and tolerability of neoadjuvant chemo-immunotherapy in UTUC and provided proof-of-concept evidence supporting further investigation. Building on these feasibility and biological activity signals, additional prospective efforts are underway. Notably, an ongoing multicenter phase II/III trial (NCT04628767) [23] is evaluating an intensified neoadjuvant strategy in cisplatin-eligible patients using dose-dense aMVAC with or without the addition of durvalumab, while a separate cohort explores durvalumab combined with gemcitabine in cisplatin-ineligible patients. In the experimental arm, durvalumab is administered intravenously on day 1 of chemotherapy cycles 1 and 3 alongside dose-dense MVAC delivered every 14 days for up to four cycles, followed by definitive RNU within 21 to 60 days in the absence of metastatic progression or unresectable disease. Although efficacy results are not yet available, this study represents a key effort to determine whether

immune checkpoint inhibition can enhance pathological response and improve oncologic outcomes beyond chemotherapy alone. An overview of the study designs, treatment regimens, and available efficacy signals from neoadjuvant chemo-immunotherapy trials in UTUC is provided in Table 4.

3.4 Adjuvant Chemotherapy (POUT Trial)

The POUT trial was the first phase III randomized study to demonstrate a benefit of perioperative systemic therapy specifically in UTUC [24]. It enrolled 261 patients with pT2-T4 and/or pN+ M0 disease following RNU and randomized them to four cycles of adjuvant gemcitabine–platinum chemotherapy (cisplatin for GFR ≥50 mL/min or carboplatin for GFR 30-49 mL/min) versus surveillance. The study population was representative of real-world practice, with two-thirds of patients harboring pT3 disease, 91% being node-negative, and approximately 64% eligible for cisplatin-based therapy.

At the time of the primary analysis, adjuvant chemotherapy significantly improved disease-free survival (DFS), with a HR of 0.45 (95% CI 0.30-0.68; p=0.0001). Three-year DFS rates were 71% in the chemotherapy arm compared with 46% in the surveillance arm, corresponding to an absolute improvement of 25%. A consistent benefit was also observed MFS (HR 0.48; 95% CI 0.31-0.74; p=0.0007), with 3-year event-free rates of 71% versus 53%. On the basis of this clear DFS advantage, the trial was stopped early following a prespecified interim analysis, which inevitably limited the number of observed death events and reduced the statistical power for OS comparisons [24].

Updated long-term results with a median follow-up of approximately 65 months confirmed the durability of benefit. Five-year DFS was 62% in the chemotherapy arm versus 45% with surveillance (HR 0.55; 95% CI 0.38-0.80; p=0.001), with an 18-month improvement in restricted mean survival time (RMST). Although OS was not the primary endpoint, a clinically meaningful signal emerged: 5-year OS was 66% with chemotherapy versus 57% with surveillance (univariable HR 0.68; 95% CI 0.46-1.00; p=0.049), and RMST analysis demonstrated an 11-month OS benefit (78 vs. 67 months; p=0.036), despite non-proportional hazards and reduced power due to early trial closure [25].

Importantly, AC did not reduce the incidence of second primary bladder tumors, suggesting that its benefit is primarily driven by prevention of systemic relapse rather than intraluminal seeding. However, patients allocated to chemotherapy were less likely to require systemic treatment at the time of recurrence compared with those under surveillance (49% vs. 63%), indicating a meaningful downstream impact on subsequent treatment burden. Subgroup analyses showed consistent DFS benefit across prespecified strata, including both cisplatin- and carboplatin-based regimens, although the trial was not powered to formally compare platinum agents.

From a safety perspective, grade ≥3 acute adverse events occurred in 44% of patients receiving chemotherapy compared with 4% in the surveillance group, with neutropenia being the most frequent toxicity (36%). No treatment-related deaths were reported, and long-term follow-up showed no clinically relevant differences in quality of life between arms.

Collectively, the POUT trial established adjuvant platinum-based chemotherapy as a standard of care for patients with high-risk UTUC following RNU, providing robust evidence of sustained DFS benefit and emerging long-term survival advantage, while also clarifying the limitations inherent to postoperative treatment delivery and trial design.

3.5 Adjuvant Immunotherapy in UTUC: An Unresolved Question

Three phase III randomized trials have evaluated adjuvant immune checkpoint inhibitors (ICIs) following radical surgery for high-risk muscle-invasive urothelial carcinoma: IMvigor010 (atezolizumab vs observation), CheckMate 274 (nivolumab vs placebo), and AMBASSADOR/KEYNOTE-123 (pembrolizumab vs observation). Although all three trials permitted enrollment of patients with UTUC, upper tract tumors consistently represented a minority of the study populations, and none of the trials was powered to assess UTUC-specific efficacy. The main design characteristics and key outcomes of these trials are summarized in Table 5.

In IMvigor010 [26], UTUC accounted for approximately 7% of enrolled patients. Within this subgroup, adjuvant atezolizumab did not improve DFS, with a HR of 1.25 (95% CI 0.57-2.74), reflecting both the absence of a treatment signal and substantial uncertainty due to the very small sample size.

CheckMate 274 [27] provided the most detailed evaluation of tumor location. While adjuvant nivolumab significantly improved DFS in the overall study population, no benefit was observed in patients with UTUC.

Specifically, the DFS hazard ratio was 1.23 (95% CI 0.74-2.05) for renal pelvis tumors and 1.56 (95% CI 0.83-2.93) for ureteral tumors, with confidence intervals crossing unity and no evidence of a favorable effect in either subgroup.
In AMBASSADOR [28], UTUC accounted for approximately 22% of enrolled patients; within this subgroup, adjuvant pembrolizumab did not demonstrate a clear DFS benefit, with a hazard ratio of 1.28 (95% CI 0.81-2.01), reflecting limited efficacy and wide confidence intervals due to small sample size.
Collectively, despite the established role of adjuvant immunotherapy in high-risk bladder urothelial carcinoma, available data do not support a clear benefit of adjuvant ICIs in UTUC. This lack of evidence is largely driven by the underrepresentation of UTUC in pivotal trials and the absence of adequately powered, disease-specific analyses, potentially compounded by biological differences between upper tract and bladder urothelial carcinomas. Accordingly, adjuvant immunotherapy in UTUC should be regarded as investigational, pending results from dedicated prospective studies.

3.6. Challenges and Future Directions in Perioperative Management

3.6.1. Predictive models to guide perioperative therapy

Accurate preoperative risk stratification remains a major challenge in UTUC, largely due to the inherent limitations of clinical staging. The absence of a clearly defined muscularis propria, sampling error associated with ureteroscopic biopsy, and the limited sensitivity of cross-sectional imaging contribute to frequent discordance between clinical and final pathological stage. As a result, a substantial proportion of patients are either overtreated with NAC despite harboring non–muscle-invasive disease, or undertreated by proceeding directly to surgery despite occult muscle invasion. This uncertainty represents a critical barrier to the rational and efficient deployment of perioperative systemic therapy.
To address this gap, several multivariable predictive models integrating routinely available preoperative variables have been developed to estimate the probability of muscle-invasive disease and to support individualized clinical decision-making. The study by Favretto et al. underscored the magnitude of the problem by demonstrating that conventional clinical risk stratification alone inadequately discriminates between organ-confined and muscle-invasive UTUC, with misclassification rates exceeding 30%. Their multivariable model (incorporating ureteroscopic biopsy grade, tumour architecture, hydronephrosis, and radiographic features) achieved a moderate but clinically meaningful discriminative performance, with an area under the receiver operating characteristic curve (AUC) of approximately 0.70, clearly outperforming any single clinical variable [29].
Crucially, decision curve analysis demonstrated that the Favaretto et al. model provided a tangible clinical net benefit over default strategies of treating all patients or treating none across a wide range of clinically relevant threshold probabilities for muscle-invasive disease. At threshold probabilities between 40% and 50%, application of the model yielded a net benefit of 0.10-0.24 compared with treating all patients, corresponding to approximately 15-24 patients spared NAC per 100 treated, without compromising the identification of ≥pT2 or node-positive disease. These findings provided early proof that model-guided patient selection could meaningfully reduce overtreatment while preserving oncologic vigilance.
More recently, this concept has been further refined and validated through the large international ROBUUST 2.0 collaborative effort. Using data from 1.558 patients with high-risk UTUC, Ditonno et al. developed and internally validated a pretreatment nomogram designed to predict muscle-invasive disease (≥pT2) at final pathology. Among the evaluated models, the biopsy-related nomogram demonstrated the highest discriminative accuracy, with an AUC of 0.74 (0.70 after internal cross-validation), and consistently outperformed guideline-based risk stratification approaches. Decision curve analysis confirmed a sustained clinical net benefit across all examined threshold probabilities, with systematic reductions in unnecessary and potentially avoidable perioperative systemic therapy [30].
From a practical perspective, at a clinically intuitive probability threshold of approximately 50%, application of the ROBUUST 2.0 nomogram would allow 17-18% of patients to be spared NAC, while missing only 6-7% of patients with true muscle-invasive disease. Even at lower thresholds (40-45%), the model preserved high sensitivity while still sparing 11-13% of patients from unnecessary NAC. These findings illustrate how predictive modeling can outperform default “treat-all” or “treat-none” strategies by aligning treatment intensity with individualized risk.
These studies demonstrate that multivariable predictive models can meaningfully improve preoperative risk stratification and support more individualized perioperative treatment decisions in UTUC. Nevertheless,

further advances are required. Future research should focus on integrating molecular biomarkers, genomic features, and artificial intelligence–based approaches with clinical and radiographic variables to enhance predictive accuracy, better capture tumor biology, and further refine patient selection for perioperative systemic therapy.

3.6.2. ctDNA and Urine Tumor DNA as Emerging Tools to Direct Perioperative Therapy in UTUC

Circulating tumor DNA (ctDNA) has emerged as a promising biomarker to improve perioperative risk stratification and guide treatment selection in UTUC, particularly in the setting of well-recognized limitations in clinical staging. In a prospective study of 50 patients with UTUC, Nakano et al. [31] demonstrated that perioperative ctDNA analysis using ultradeep sequencing could identify a subgroup of patients with markedly worse oncologic outcomes despite apparently localized disease at diagnosis. Among patients with clinically localized UTUC, preoperative ctDNA positivity (defined as a ctDNA fraction >2%) was the only preoperative variable independently associated with inferior RFS. On multivariable analysis, a ctDNA fraction >2% was associated with a more than fourfold increased risk of recurrence (HR 4.57; 95% CI 1.43-14.54; p = 0.010), outperforming conventional clinicopathologic and imaging-based staging parameters. Consistent with this finding, Kaplan-Meier analyses showed profoundly inferior outcomes in ctDNA-positive patients, with significantly worse RFS (HR 13.75; 95% CI 3.50-54.03) and OS (HR 32.93; 95% CI 7.87-13.78), underscoring the strong prognostic discrimination conferred by ctDNA status.

Complementary evidence comes from a prospective study by Tamura et al., which evaluated individualized ctDNA monitoring using digital PCR in 23 patients undergoing RNU [32]. In this cohort, postoperative ctDNA dynamics were closely associated with recurrence risk. All patients who developed intravesical recurrence (100%) were ctDNA-positive in urine at the time of relapse, compared with detection rates of 60% using urine cytology and 30% with CT imaging. Urinary ctDNA identified recurrence with a mean lead time of approximately 60 days (range 0-202 days) before conventional clinical detection. On multivariable analysis, failure to achieve a ≥95% reduction in urinary ctDNA levels early after surgery was independently associated with significantly shorter RFS, supporting ctDNA clearance as a robust surrogate marker of effective local disease control.

These findings support ctDNA and urine tumor DNA as biologically informative, minimally invasive tools that can complement conventional staging and imaging in UTUC. In clinical practice, ctDNA profiling holds promise for identifying patients most likely to benefit from perioperative systemic therapy, enabling earlier detection of residual or recurrent disease, and sparing low-risk patients from unnecessary treatment (thereby advancing a more personalized, risk-adapted perioperative management strategy).

3.6.3. Unresolved clinical scenarios for perioperative treatment

Several key clinical contexts remain poorly defined despite accumulating evidence for neoadjuvant and adjuvant therapy:

Lymphovascular invasion: is present in approximately one quarter of UTUC cases and is consistently associated with worse survival and lower likelihood of downstaging after NAC [33]. However, whether all positive-nodes patients should systematically receive perioperative chemotherapy is unknown, and current trials have not been powered to address this question.

Locally advanced and non-organ-confined disease: Patients with pT4 or gross local invasion have the highest risk of relapse, yet many present with impaired renal function or comorbidities that limit cisplatin use. The true magnitude of benefit from NAC or adjuvant therapy in this subset, particularly when carboplatin is used, remains uncertain.

Histologic variants: Accounts for roughly 10-15% of UTUC [34] and is associated with aggressive behaviour. Data on perioperative chemotherapy in these variants are sparse and often extrapolated from bladder cancer; no dedicated prospective evidence exists.

Clinically node-positive disease: Induction chemotherapy followed by consolidative RNU is frequently used in cN+ UTUC by analogy with bladder cancer, but its benefit is supported only by small retrospective series [35]. Optimal regimens, duration of therapy and the role of consolidative lymphadenectomy are all undefined.

Contribution of lymphadenectomy: Extended lymph node dissection is suggested by current EAU guidelines for patients with high-risk UTUC, although the optimal template remains undefined and the strength of recommendation is weak [36]. Its interaction with perioperative chemotherapy has never been formally

evaluated. In trials such as POUT [24], lymphadenectomy was performed inconsistently and was not standardized, making it impossible to clearly determine the respective contributions of surgery and systemic therapy.

4. Conclusions

Perioperative systemic therapy has become a key component of management for patients with high-risk UTUC. Prospective phase II trials support the feasibility and biological activity of neoadjuvant platinum-based chemotherapy, with pathological response (particularly downstaging to ≤ypT1N0 or pathologic complete response) emerging as a reproducible surrogate of long-term benefit across multicenter and population-level datasets [5,6]. In parallel, the randomized phase III POUT trial [24] established adjuvant platinum-based chemotherapy as a standard of care after RNU, providing durable disease-control benefit and an emerging long-term survival signal. By contrast, current evidence does not demonstrate a clear benefit for adjuvant immune checkpoint inhibition in UTUC subgroups, and neoadjuvant immunotherapy monotherapy appears insufficiently effective.

Despite these advances, key gaps remain. The optimal sequencing of perioperative chemotherapy (neoadjuvant vs adjuvant) is still unresolved and is being directly addressed by the ongoing URANUS trial [18]. Moreover, the clinical deployment of neoadjuvant strategies is constrained by imperfect preoperative staging, highlighting the need for better selection tools. Multivariable predictive models provide proof-of-concept that model-guided selection may reduce overtreatment while maintaining oncologic vigilance [30], and emerging biomarkers such as ctDNA and urine tumor DNA offer a clinically actionable framework to refine risk stratification, detect minimal residual disease, and potentially guide escalation or de-escalation of perioperative therapy [31,32].

More recently, neoadjuvant chemo-immunotherapy combinations have shown biological activity and manageable toxicity in early-phase studies [26-28]. While definitive evidence from randomized controlled trials is still lacking, these approaches represent a promising strategy that requires validation in ongoing randomized studies to define their oncological benefit.

Future progress will depend on integrating prospective trials with biomarker-driven and AI-enhanced risk models to personalize treatment intensity, identify patients most likely to benefit from perioperative therapy, and clarify unresolved clinical scenarios.

Statements

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

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Figure 1. PRISMA flow diagram of the literature search and study selection process.

Identification Total (n = 150)

Records identified through database searching
PubMed (n = 78)
Embase (n = 56)
Clinical Trials (n = 16)

Screening
Records after duplicates removed (n = 104)
Records screened (n = 104)
Records excluded (n = 48)

Eligibility
Full-text articles assessed for eligibility (n = 56)
Full-text articles excluded (n = 20)

Included
Studies included in qualitative synthesis (n = 36)

Table 1. Comparison of Phase II Neoadjuvant Chemotherapy Trials in UTUC

	Margulis et al. (2020) [5] **NCT02412670 - ECOG-ACRIN Cancer Research Group**	**Coleman et al. (2023) [6]** **NCT01261728**
Study design	Phase II, prospective, multicentre (ECOG-ACRIN)	Phase II, prospective, multicentre (4 centres)
Population	HG localized UTUC; CrCl ≥ 30 mL/min	HG cT2–T4a N0/X M0; CrCl ≥ 55 mL/min
Treatment	aMVAC × 4 cycles if CrCl > 50 mL/min; GC-carboplatin if CrCl 30–50 mL/min	Gemcitabine + cisplatin (split-dose) × 4 cycles
Sample size	36 patients (29 evaluable for aMVAC arm)	57 patients
Primary endpoint	Pathologic complete response (pCR, ypT0N0)	Pathologic response (< ypT2N0)
Result for primary endpoint	pCR 14 % (aMVAC); 17 % (GCa)	< ypT2N0 63 %; pCR 19 %
Grade 3–4 adverse events	23 % (aMVAC); 50 % (GCa)	74 % overall (manageable)
Median follow-up	1.76 years (21.1 months)	3.1 years

2-year progression-free survival	Not reached	89 %
Comments	Met predefined activity threshold; good feasibility	Met efficacy threshold; favourable long-term outcomes

HG = High grade; CrCl = Creatinine clearance; aMVAC = Accelerated methotrexate, vinblastine, doxorubicin, and cisplatin; GC = Gemcitabine and cisplatin; GCa = Gemcitabine and carboplatin; pCR = Pathologic complete response; ypT0N0 = No residual tumor (T0) and negative lymph nodes (N0) after neoadjuvant therapy; < ypT2N0 = Pathologic stage less than T2 with negative lymph nodes; AE = Adverse events; PFS = Progression-free survival

Table 2. Observational and propensity-adjusted studies of NAC in UTUC.

Author (Year)	Design / N	Adjustment method	Key findings
Chen L (2020) [9]	Retrospective multicentre; 48 NAC vs 72 no NAC	Propensity score matching (1:1; 37 vs 37)	NAC improved DFS and OS (HR 0.25 and 0.22) and increased downstaging rates.
Meng X (2019) [10]	Retrospective observatonal single-institution cohort study; 31 NAC + RNU	Propensity score matching, inverse probability of treatment weighting (IPTW)	High rates of pathological response and downstaging following platinum-based NAC in patients with high-grade UTUC
Tae JH (2022) [11]	Nationwide cohort (Korean database); 8.705 total; 94 NAC, 1.984 AC	Inverse probability of treatment weighting	NAC improved OS and CSS compared with adjuvant chemotherapy or surgery alone; benefit maintained after weighting.
Tuderti G (2024) [12] ROBUUST 2.0 Registry	Real-world multicentre ≈ 2.000 patients (2015–2022)	Multivariable adjustment	NAC in advanced and node-positive UTUC improved CSS and OS vs surgery alone.

Abreviations: NAC = Neoadyuvant Chemotherapy; DFS = Disease-free survival; OS = Overall survival; HR = Hazard ratio; CSS = Cancer-specific survival; RNU = radical nephrouretectomy; AC = Adyuvant chemotherapy.

Table 3. Comparative overview of meta-analyses evaluating NAC in UTUC.

Meta-analysis	Design & N of studies	Population included	Main findings	Sources of heterogeneity and bias
Leow 2020 [15]	Systematic review + quantitative synthesis	High-risk UTUC; stricter study selection	pCR≈11%, pPR≈43%; improved OS/CSS in comparative studies	Inconsistent definitions of pathological response; variable lymph node dissection; overlapping institutional cohorts; varied follow-up durations
Oswald 2022 [16]	Meta-analysis of controlled studies (NAC vs RNU alone)	High-risk UTUC with internal control groups	Higher odds of downstaging (OR~5) and pCR; improved adjusted OS/CSS	Retrospective designs; variability in surgical approach; no uniform pathological endpoints; signal of publication bias
Deb 2024 [17]	Largest pooled analysis; 21 studies; >14.000 patients	Broad definition of “high-risk”; multiple regimens	pCR ~10%; downstaging ~42%; reduced advanced pT stage after NAC	Extremely heterogeneous populations; wide variation in regimens and number of cycles; long inclusion periods; inconsistent adjustment; probable duplication of patient cohorts

Table 4. Summary of Neoadjuvant Chemo-Immunotherapy Trials in High-Risk UTUC

	iNDUCT (Phase II, NCT04617756) [21]	**Phase II/III Trial NCT04628767 [23]**
Study type	Phase II, single-arm, multicenter trial	Phase II/III, randomized controlled trial
Population	High-risk non-metastatic UTUC; cisplatin-eligible and ineligible cohorts	HG UTUC; stratified by cisplatin eligibility
Interventions	Durvalumab + gemcitabine/cisplatin or durvalumab + gemcitabine/carboplatin (cis-ineligible) ×4 cycles	Cisplatin-eligible: aMVAC ± durvalumab
Comparator	None (single-arm)	aMVAC alone vs durvalumab + aMVAC (randomized; cis-eligible)
Primary endpoint	pCR	Cis-eligible: Event-free survival Cis-ineligible: pCR
Key results	pCR 13% (cisplatin cohort), 5% (carboplatin cohort); ≤ypT1	No published results available

	in 50% and 42%; acceptable safety (JCO 2025)	
Surgery timing	RNU 4–6 weeks after NAC	RNU 21–60 days after systemic therapy
Status	Completed phase II; basis for planned iNDUCT-3	Ongoing; no data published

NAC = Neoadjuvant chemotherapy; RNU = Radical nephroureterectomy; OS = Overall survival; CSS = Cancer-specific survival; PFS = Progression-free survival; pCR = Pathologic complete response; pPR = Pathologic partial response; OR = Odds ratio

Table 5. Adjuvant Immunotherapy Trials Including UTUC Subgroups (Summary)

Trial	Agent	Overall DFS Result	UTUC Proportion	UTUC Subgroup HR (DFS)	Interpretation
IMvigor010 [26] NCT02450331	Atezolizumab vs Observation	Negative (HR 0.89)	7%	1.25 (95% CI 0.57-2.74)	No benefit; CI very wide due to small sample
CheckMate 274 [27] NCT02632409	Nivolumab vs Placebo	Positive (HR 0.70)	20-22%	Renal pelvis: 1.23 (0.67-2.23); Ureter: 1.56 (0.70-3.48)	No benefit in UTUC subgroups; underpowered
AMBASSADOR [28] NCT03244384 / KEYNOTE-123	Pembrolizumab vs Observation	Positive (HR 0.73)(overall)	22%	Not reported	No UTUC-specific HR; subgroup described as inconclusive

UTUC = Upper tract urothelial carcinoma; DFS = Disease-free survival; HR = Hazard ratio; CI = Confidence interval