Clinical Efficacy and Safety of Radical Nephroureterectomy With Versus Without Template Lymph Node Dissection in High-Risk Upper Tract Urothelial Carcinoma: A Multicenter, Prospective, Randomized Controlled Clinical Trial

Study Protocol

Protocol Number:	
Protocol Version Number:	V1.0
Protocol Version Date:	August 20, 2025
Principal Investigators:	
Sponsor:	Tianjin Medical University Second Hospital

Principal Investigator Signature Page

I confirm that this clinical study is an Investigator-Initiated Trial (IIT). The principal investigator of this clinical study will simultaneously assume the relevant responsibilities of both the investigator and the sponsor as stipulated in GCP.

I will diligently fulfill the responsibilities of both the sponsor and the investigator in accordance with GCP, personally participate in, and directly guide this clinical study. I confirm this study protocol. I agree to perform the relevant duties in accordance with Chinese laws, the Declaration of Helsinki, GCP, and this clinical study protocol. I confirm that this study protocol and any subsequent protocol amendments must be approved by the Ethics Committee before implementation. I will keep this study protocol and documents and information related to this study confidential.

Research Unit:Tianjin Medical University Second Hospital

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Principal Investigator (Printed Name)	Principal Investigator (Signature)	Signature Date (Year/Month/Day)

Protocol Summary

Study Title	Clinical Efficacy and Safety of Radical Nephroureterectomy With Versus Without Template Lymph Node Dissection in High-Risk Upper Tract Urothelial Carcinoma: A Multicenter, Prospective, Randomized Controlled Clinical Trial
Protocol Number	
Protocol Version Number	V1.0
Protocol Version Date	2025-08-04
Clinical Study Type	Registrational Clinical Trial
Clinical Study Registration	Investigator-Initiated Trial, IIT
Clinical Trial Approval Document	
Clinical Study Unit	Tianjin Medical University Second Hospital
Funder	
Study Population	Patients clinically diagnosed with high-risk (cT2-4N0-1M0 or cT1N1M0) upper tract urothelial carcinoma (UTUC) who are planned to undergo radical nephroureterectomy.
Study Objectives	**Primary Objectives:** 1) Compare the impact of radical nephroureterectomy combined with template lymph node dissection versus radical nephroureterectomy alone on disease-free survival (DFS) and overall survival (OS) in patients with high-risk non-metastatic UTUC. 2) Evaluate and compare the surgical safety between the two groups, including perioperative complications (according to Clavien-Dindo classification), operative time, intraoperative blood loss, and hospital stay.

	Secondary Objectives: 1）Compare non-urothelial tract recurrence-free survival (NU-RFS), intravesical recurrence-free survival (IV-RFS), and cancer-specific survival (CSS) between the two groups. 2）Establish a lymph node metastasis (pN+) map for UTUC at different sites in the high-risk UTUC population through template lymph node dissection (LND).
	Exploratory Objectives: 1）Utilize prospectively collected tumor tissues to explore molecular biomarkers for predicting prognosis through Bulk-RNA sequencing. 2）Utilize prospectively collected radiomics data from renal ureter contrast-enhanced CT, tumor size/location, retroperitoneal/pelvic lymph node size/location, and clinical symptoms to establish a nomogram for predicting lymph node metastasis.
Study Design	This is a multicenter, prospective, open-label, randomized controlled clinical trial.
Sample Size	**150 cases**
Study Endpoints	**Primary Endpoints:** 1) Disease-free survival (DFS): Defined as the time from randomization to the first recorded recurrence at any site (local, regional lymph nodes, distant metastasis), new urothelial carcinoma in the contralateral upper tract or bladder, or death from any cause, whichever occurs first. Overall survival (OS): Defined as the time from randomization to the recorded death from any cause. 2) Perioperative complications, intraoperative blood loss, performance status (Karnofsky score), and hospital stay. **Secondary Endpoints:** 1) NU-RFS: Defined as the time from randomization to the first recorded local, regional lymph node, distant metastasis recurrence, or death from any cause, whichever occurs first. IV-RFS: Defined as the time from randomization to the first recorded new urothelial carcinoma in the contralateral upper tract or bladder, or death from any cause, whichever occurs first. CSS: Defined as the time from randomization to the recorded death due to urothelial carcinoma. 2) Lymph node metastasis map: Positive rate (pN+%) of lymph nodes at each template dissection site. 3) Identify efficacy biomarkers for DFS, OS, and CSS using Bulk-RNA sequencing technology.

	4) Lymph node metastasis prediction: Establish a nomogram for predicting lymph node metastasis based on prospectively collected radiomics data from whole-abdomen triple-phase contrast-enhanced CT, tumor size/location, lymph node size/location at each template dissection site, and clinical symptoms.
Surgery	**1) Randomization Groups:** Experimental Intervention (Group A): Nephroureterectomy + Template Lymph Node Dissection. Control Intervention (Group B): Nephroureterectomy + Dissection of only lymph nodes visible on imaging or intraoperatively (>1 cm). **2) Lymph Node Dissection Template (Group A only):** Renal Pelvis & Upper Ureter Tumors: Dissect renal hilum, para-aortic or para-caval lymph nodes (depending on affected side). Superior border: level of the central adrenal vein (right) or superior border of adrenal gland; Inferior border: bifurcation of aorta or vena cava. Mid-Ureter Tumors: Extend the dissection template downward from the renal pelvis/upper ureter template to below the tumor level, including common iliac and external iliac nodes. Lower Ureter Tumors: Dissect pelvic lymph nodes, including common iliac, external iliac, internal iliac, and obturator lymph node regions. **3) Surgical Requirements:** Surgical approach (open, laparoscopic, or robot-assisted) is determined by the surgeon based on the patient's specific condition and technical expertise; the lymph node dissection scope must strictly follow the protocol-defined template. Radical Nephroureterectomy (RNU): Both groups require complete resection of the affected kidney, perirenal fat, and the entire ureter, including a bladder cuff excision. Lymph Node Dissection (LND): Group A (Experimental): Must strictly execute the corresponding template lymph node dissection based on tumor location. Group B (Control): Template lymph node dissection is not performed. If clearly enlarged suspicious lymph nodes (>1 cm) are found intraoperatively, resection of visible lymph nodes is allowed for pathological staging, but template dissection is not performed.
Study Procedures	This clinical study includes three main phases: screening, treatment, and follow-up. Screening Period: 1) From signing informed consent until randomization. 2) The screening period should not exceed 14 days. Treatment Period: 1) Surgery is performed after randomization, and perioperative data are recorded up to 30 days postoperatively. Follow-up Period: 1) Safety Follow-up: Subjects undergo safety follow-up postoperatively, tracking adverse events (AEs) until resolution or stabilization, or return to baseline levels. 2) Survival Follow-up: Conducted every 3 months, recording survival status until subject death, loss to follow-up, withdrawal of consent, completion of 5-year survival follow-up, or study end, whichever occurs first.

	3) Tumor Progression Follow-up: Starts postoperatively. Survival and recurrence data are collected via outpatient review and telephone follow-up. Within 2 years postoperatively: imaging (CT/MRI/US) and urinary cytology every 3 months, cystoscopy every 6 months. Years 3-5: intervals extended to 6 months. After 5 years: annual review until patient death, loss to follow-up, withdrawal of consent, or study end (maximum follow-up 10 years), for assessing DFS, CSS, and OS. (Within 5 years, contrast-enhanced CT/MRI annually, or as deemed necessary by the investigator).
Inclusion Criteria	Patients meeting all of the following criteria may be enrolled: 1) Signed written Informed Consent Form (ICF). 2) Age >18 years at the time of signing ICF, either gender. 3) Clinical diagnosis of unilateral UTUC by imaging (contrast-enhanced CT or MRI) and/or ureteroscopic biopsy/urinary cytology, and planned to undergo radical nephroureterectomy. 4) Clinical assessment indicates that the tumor and regional lymph nodes can be completely resected, and with at least one of the following high-risk features: a) Locally advanced: Preoperative imaging assessment of cT2 stage or higher (i.e., tumor invades muscularis propria or deeper). b) High-grade: Preoperative ureteroscopic biopsy pathology confirms high-grade urothelial carcinoma (or with squamous differentiation/sarcomatoid differentiation). c) Moderate to severe hydronephrosis: Ipsilateral moderate or severe hydronephrosis due to tumor obstruction. d) Large tumor size: Maximum tumor diameter >2cm on imaging. e) cN1: Imaging suggests regional lymph node short axis >1cm, and the investigator judges it as resectable. 5) Measurable lesion according to RECIST v1.1 criteria. 6) Eastern Cooperative Oncology Group (ECOG) performance status score: 0~1. 7) Adequate function of major organs meeting the following requirements (excluding use of any blood components or growth factors within 14 days): Normal bone marrow reserve: neutrophils $\geq$ 1500/mm^3, platelets $\geq$ 100,000/mm^3, hemoglobin $\geq$5.6 mmol/L (9 g/dL); Normal renal function: serum creatinine $\leq$1.5 mg/dL and/or creatinine clearance $\geq$60 ml/min; Normal liver function: bilirubin $\leq$1.5xULN, AST & ALT $\leq$1.5xULN. 8) Non-sterilized or women of childbearing potential must use a medically approved contraceptive method during the study treatment and for 3 months after treatment ends (e.g., IUD, oral contraceptives, condoms); Non-sterilized women of childbearing potential must have a negative serum or urine HCG test within 7 days

	before study enrollment; must be non-lactating; Non-sterilized men of childbearing potential must agree to use a medically approved contraceptive method with their partner during the study treatment and for 3 months after treatment ends. 9) The subject voluntarily joins the study, has good compliance, and cooperates with safety and survival follow-up.
Exclusion Criteria	**Patients with any of the following cannot be enrolled:** 1) Previous receipt of any anti-tumor therapy for UTUC, including chemotherapy, radiotherapy, immunotherapy, or targeted therapy. 2) Previous or concurrent muscle-invasive bladder urothelial carcinoma. 3) Preoperative imaging assessment indicates unresectable regional lymph nodes: lymph nodes fused into a massive conglomerate, or completely encasing the abdominal aorta/inferior vena cava/pelvic vessels preventing safe separation. 4) Known bilateral UTUC or genetic diseases that clearly increase the risk of contralateral upper tract tumors, such as Lynch Syndrome. 5) Diagnosis of other active malignancies within the past 5 years (except for cured skin basal cell carcinoma, skin squamous cell carcinoma, or cervical carcinoma in situ with no recurrence within 5 years). 6) Presence of any active autoimmune disease or history of autoimmune disease (including but not limited to: autoimmune hepatitis, interstitial pneumonia, uveitis, enteritis, hepatitis, hypophysitis, vasculitis, nephritis, hyperthyroidism, hypothyroidism; subjects with vitiligo or childhood asthma that has completely resolved and requires no intervention in adulthood may be included; asthma requiring bronchodilator intervention cannot be included). 7) Subject is using immunosuppressants for immunosuppressive purposes and continues use within 2 weeks prior to enrollment. 8) Poorly controlled cardiac clinical symptoms or diseases, such as: a) NYHA Class II or above heart failure; b) Unstable angina; c) Myocardial infarction within 1 year; d) Clinically significant supraventricular or ventricular arrhythmias requiring treatment or intervention. 9) Coagulation abnormalities (PT>16s, APTT>43s, TT>21s, Fibrinogen<2g/L), bleeding tendency, or receiving thrombolytic or anticoagulant therapy. 10) Preoperative presence of esophageal varices, active gastric/duodenal ulcer, ulcerative colitis, portal hypertension, or other gastrointestinal diseases, or active bleeding from an unresected tumor, or other conditions deemed by the investigator likely to cause gastrointestinal bleeding or perforation. 11) History or current presence of severe hemorrhage (>30ml within 3 months), hemoptysis (>5ml of fresh blood within 4 weeks), or thromboembolic events

	(including stroke and/or transient ischemic attack) within 12 months. 12) Active infection at the time of screening, or unexplained fever >38.5° C during screening or before the first dose. 13) Abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 4 weeks prior to surgery. 14) Objective evidence of history or current presence of pulmonary fibrosis, interstitial pneumonia, pneumoconiosis, radiation pneumonitis, drug-related pneumonia, severely impaired pulmonary function, etc. 15) Congenital or acquired immunodeficiency, such as HIV infection, or active hepatitis (liver enzymes not meeting inclusion criteria; for hepatitis B: HBV DNA ≥10^4 copies/ml; for hepatitis C: HCV RNA ≥10^3 copies/ml); chronic HBV carriers with HBV DNA ≥2000 IU/ml (≥10^4 copies/ml) can only be enrolled if they receive concurrent antiviral therapy during the trial. 16) Subject is participating in another clinical study or less than 1 month has passed since the end of the previous clinical study; subject may receive other systemic anti-tumor therapy during the study period. 17) Known history of drug abuse, alcoholism, or drug addiction; subject is unable or unwilling to bear the self-paid portion of examination and treatment costs; the investigator considers exclusion from the study for other reasons, e.g., other serious diseases (including mental illness) requiring combined treatment, severe laboratory abnormalities, or family/social factors that may affect subject safety, or data/sample collection.
Withdrawal Criteria	1) The subject or their legal representative requests early withdrawal. 2) The investigator, based on professional judgment, believes that continued participation may harm the subject's health. 3) Cancellation of the planned radical nephroureterectomy or inability to perform it for any reason. 4) Subject is lost to follow-up or unable to complete key protocol-specified follow-up due to poor compliance. 5) The investigator deems it necessary to withdraw the subject. All withdrawn subjects should be followed up according to the study protocol, and follow-up results recorded, unless the patient withdraws consent and refuses follow-up.
Concomitant Medications/ Therapies	**Permitted Concomitant Medications/Therapies:** Supportive care; topical analgesics; all adverse reactions should be actively treated, especially those related to postoperative complications.

Safety Evaluation	Safety evaluation indicators include adverse events observed during the study, changes in laboratory tests, vital signs, ECG, lower extremity venous ultrasound results before and after treatment, intraoperative blood loss, postoperative complications, time to discharge, etc. Record the name, start and end time, measures taken, and outcome of all AEs during the study. Grade severity of AEs according to NCI CTCAE v5.0; grade severity of postoperative complications according to Clavien-Dindo classification
Efficacy Evaluation	1) Assess postoperative DFS and PFS (if applicable) according to RECIST v1.1 criteria via regular imaging (chest CT, lower abdomen contrast-enhanced CT/MRI), record OS. 2) Evaluate surgical outcomes based on pathological results and perioperative conditions. 3) Identify efficacy biomarkers using Bulk-RNA data.
Statistical Methods	1) Primary endpoints DFS, OS and secondary survival endpoints NU-RFS, IV-RFS, and CSS will be estimated using the Kaplan-Meier method and compared between groups using the log-rank test. 2) Multivariate analysis will be performed using the Cox proportional hazards model. 3) Categorical variables (e.g., complication rate, pN+ rate) will be compared using the chi-square test. 4) Continuous variables (e.g., operative time, blood loss) will be compared using the t-test. 5) In this study, unless otherwise specified, data will be summarized using descriptive statistics according to the following general principles. Measurement data will be summarized using mean, standard deviation, median, maximum, and minimum; count data will be summarized using frequency and percentage. 6) Safety Analysis: Adverse events will be summarized using frequency and percentage; laboratory tests (blood routine, blood biochemistry, etc.), ECOG, vital signs, and ECG will be summarized using descriptive statistics. 7) Quality of Life Analysis: Paired t-test will be used to compare changes. All tests are two-sided, and a p-value <0.05 is considered statistically significant.
Treatment Discontinuation	Defined as termination of treatment for any reason, e.g., inability to perform the surgical procedure, intolerance, or early withdrawal. Safety follow-up must still be completed after treatment discontinuation to assess AE resolution.
Study Completion	Defined as the last subject completing follow-up, or early withdrawal from follow-up.

Study Termination	1) The investigator identifies unexpected, significant, or unacceptable risks to subjects. 2) A major design flaw is discovered during study execution. 3) The experimental treatment is ineffective, or the investigator judges that continuing the study is meaningless. 4) The research institution or ethics committee decides to terminate the clinical study early.
Study Timeline	Estimated date of first subject enrollment: September 2025 Estimated date of last subject enrollment: August 2027 Estimated study completion date: August 2032