Template Lymph Node Dissection for Tumor Control in High-Risk Renal Cell Carcinoma: A Prospective, Open-Label, Multicenter, Randomized Controlled Trial

Study Protocol

Protocol Number:	
Protocol Version Number:	V1.0
Protocol Version Date:	August 10, 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	Template Lymph Node Dissection for Tumor Control in High-Risk Renal Cell Carcinoma: A Prospective, Open-Label, Multicenter, Randomized Controlled Trial
Protocol Number	
Protocol Version Number	V1.0
Protocol Version Date	2025-08-10
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 with renal cell carcinoma (RCC) amenable to nephrectomy (clinical stage cT3-4N0-1M0), as well as M1 patients whose metastatic lesions can be rendered M0 status (No Evidence of Disease, NED) with local therapy.
Study Objectives	**Primary Objectives:** 1) To compare the impact of nephrectomy combined with template lymphadenectomy versus nephrectomy alone on Overall Survival (OS) and Disease-Free Survival (DFS) in patients with high-risk RCC at risk of recurrence or progression. 2) To evaluate and compare the surgical safety between the two groups, including perioperative complications (graded by the Clavien-Dindo classification), operation time, intraoperative blood loss, and hospital stay.

	Secondary Objectives: 1）To compare Cancer-Specific Survival (CSS) between the two groups. 2）To quantify the number of lymph nodes retrieved and the rate of lymph node metastasis (pN+%) in the following specific template regions: right renal hilum, para-supravenous caval region, para-infravenous caval region, left renal hilum, para-supra-aortic region, para-aortic region.
	Exploratory Objectives: 1）To utilize prospectively collected tumor tissues and Bulk-RNA sequencing technology to explore potential molecular biomarkers predictive of lymph node metastasis or prognosis. 2）To develop a nomogram for predicting lymph node metastasis based on prospectively collected radiomics data (triple-phase contrast-enhanced abdominal CT, non-contrast MRI), tumor size/location, retroperitoneal/renal hilar lymph node size/location, and clinical symptoms.
Study Design	This is a multicenter, prospective, open-label, randomized controlled clinical trial.
Sample Size	**220 cases**
Study Endpoints	**Primary Endpoints:** 1) Disease-Free Survival (DFS):Defined as the time from randomization until the first documented occurrence of disease recurrence (local, regional, or distant metastasis), a second primary renal cancer, or death from any cause. 2) Overall Survival (OS):Defined as the time from randomization to death from any cause. For subjects lost to follow-up, the last follow-up date will be used as the censoring time. 3)Perioperative complications, intraoperative blood loss, ECOG Performance Status, and hospital stay. **Secondary Endpoints:** 1) Cancer-Specific Survival (CSS) 2) Number of lymph nodes retrieved and lymph node positive rate (pN+%) from each defined template region.ymph node metastasis map: Positive rate (pN+%) of lymph nodes at each template dissection site. 3) Exploration of biomarkers for DFS, CSS, and OS based on Bulk-RNA data. 4) Prediction of lymph node metastasis: Developing a predictive nomogram based on prospectively collected radiomics data from triple-phase contrast-enhanced abdominal CT, plain MRI, tumor size/location, retroperitoneal/hilar lymph node size/location, and clinical symptoms.

Surgery	**1) Randomization Groups:** Experimental Intervention (Group A): Nephrectomy + Template Lymph Node Dissection. Control Intervention (Group B): Nephrectomy + resection of radiologically or intraoperatively visible lymph nodes >1cm. **2) Lymph Node Dissection Template:** Left-side Template: Lymphatic tissue anterior and lateral to the abdominal aorta from the diaphragmatic crus to the aortic bifurcation, including the hilar lymph nodes. Right-side Template: Lymphatic tissue surrounding the inferior vena cava (IVC) and between the IVC and abdominal aorta from the liver edge of the IVC to the iliac vein bifurcation, including the hilar lymph nodes. **3) Surgical Requirements:** The surgical approach (open, laparoscopic, or robot-assisted) will be determined by the surgeon based on the patient's specific condition and the surgeon's expertise. The extent of lymph node dissection must strictly adhere to the protocol-defined template.
Study Procedures	This clinical study consists of three main phases:Screening, Treatment, and Follow-up. Screening Period: 1) From signing the Informed Consent Form (ICF) until randomization. 2)The screening period should not exceed 14 days. Treatment Period: 1)Surgical treatment after randomization. Perioperative data will be recorded up to 30 days post-surgery. 2) At the end of the treatment period, the investigator will recommend subsequent therapy. Based on patient preference, adjuvant therapy may be chosen for 1 year (17 cycles). If the patient agrees to adjuvant therapy and chooses Toripalimab, one cycle of the drug will be provided free of charge by the study. Follow-up Period: 1)Safety Follow-up: Safety follow-ups will be conducted at the end of each adjuvant treatment cycle and post-surgery, tracking Adverse Events (AEs) until resolution, stabilization, or return to baseline. 2)urvival Follow-up: Conducted every 3 weeks to document survival status until subject death, loss to follow-up, withdrawal of ICF, completion of 2-year survival follow-up, or study end, whichever occurs first. 3)Tumor Progression Follow-up: Begins post-surgery. Survival and recurrence data are collected via outpatient reviews and telephone follow-ups. Imaging (CT/MRI) will be performed every 3 months in the first year, every 6 months from years 2-5, and annually after 5 years until patient death, loss to follow-up, withdrawal of ICF, or study end (maximum follow-up 10 years), for DFS, OS, and CSS assessment.
Inclusion Criteria	Patients meeting all of the following criteria may be enrolled:

	1) Sign a written Informed Consent Form (ICF). 2) Age >18 years at the time of ICF signing, either sex. 3) Preoperative typical imaging evaluation and systemic health assessment indicate suitability for nephrectomy and nephrectomy combined with template lymph node dissection. 4) Clinical stage cT3-4 N0-1 M0 or M1 disease rendered M0 (NED) after local therapy (AJCC 8th ed.), specifically meeting at least ONE of the following high-risk criteria: a)Presence of radiologically visible lymph nodes >1cm. b) M1 disease rendered radiologically M0 (NED) after local therapy. c) Radiologically determined rT4 stage. OR meeting at least TWO of the following high-risk criteria: a)Renal vein or inferior vena cava tumor thrombus. b)Nuclear grade 3-4 and/or sarcomatoid differentiation and/or coagulative tumor necrosis. c)Tumor size ≥10 cm. d)Hematuria and local symptoms (including microscopic/gross hematuria, pain, etc.). 5) Measurable disease as per RECIST v1.1 criteria. 6) Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1. 7) Adequate organ function (without use of blood components/growth factors within 14 days):Normal bone marrow reserve function.Bone marrow: Neutrophils ≥ 1,500/mm³ , Platelets ≥100,000/mm³ , Hemoglobin ≥9 g/dL (5.6 mmol/L).Renal: Serum creatinine ≤1.5 mg/dL and/or Creatinine clearance ≥60 mL/min.Hepatic: Bilirubin ≤1.5 × ULN, AST & ALT ≤1.5 × ULN. 8) For non-sterilized or premenopausal women: Use of medically approved contraception during and for 3 months after the study; negative serum/urine HCG test within 7 days before enrollment; non-lactating. For non-sterilized men: Agreement to use medically approved contraception with their spouse during and for 3 months after the study. 9) Subject voluntarily joins the study, has good compliance, and agrees to safety and survival follow-up.
Exclusion Criteria	Patients with any of the following cannot be enrolled: 1) Prior radiotherapy, chemotherapy, long-term/high-dose corticosteroid therapy, surgery, or molecular targeted therapy for RCC. 2) History or presence of another active malignancy (except for those controlled

	with minimal impact on 2-year survival). 3) Deemed more suitable for partial nephrectomy or ablation by Multidisciplinary Team (MDT) assessment. 4) Preoperative imaging indicates unresectable regional lymph nodes: massive confluent nodal masses or complete encasement of aorta/IVC precluding safe separation. 5) Known bilateral RCC or hereditary RCC syndrome (e.g., VHL, Birt-Hogg-Dubé). 6) Diagnosis of other active malignancies within the past 5 years (except cured basal cell carcinoma, squamous cell carcinoma of the skin, or cervical carcinoma in situ with no recurrence within 5 years). 7) Any active autoimmune disease or history of autoimmune disease (e.g., autoimmune hepatitis, interstitial pneumonia, uveitis, enteritis, hepatitis, hypophysitis, vasculitis, nephritis, hyperthyroidism, hypothyroidism; Vitiligo or childhood asthma in complete remission is allowed; asthma requiring bronchodilators is excluded). 8) Use of immunosuppressive agents for immunosuppression purposes within 2 weeks prior to enrollment. 9) Poorly controlled cardiac symptoms/diseases: a) NYHA Class II+ heart failure, b) Unstable angina, c) Myocardial infarction within 1 year, d) Clinically significant supraventricular/ventricular arrhythmia requiring treatment/intervention. 10) Coagulopathy (PT>16s, APTT>43s, TT>21s, Fbg<2g/L), bleeding tendency, or undergoing thrombolysis/anticoagulation therapy. 11) Pre-existing conditions with risk of bleeding (e.g., esophageal varices, active gastric/duodenal ulcer, ulcerative colitis, portal hypertension) or active bleeding from unresected tumors, or other conditions deemed by investigator to risk GI bleeding/perforation. 12) History of severe bleeding (>30 mL within 3 months), hemoptysis (>5 mL fresh blood within 4 weeks), or thromboembolic events (including stroke/TIA) within 12 months. 13) Active infection or unexplained fever >38.5 ° C during screening/before first dose. 14) Abdominal fistula, gastrointestinal perforation, or abdominal abscess within 4 weeks before surgery. 15) History or current objective evidence of pulmonary fibrosis, interstitial pneumonia, pneumoconiosis, radiation pneumonitis, drug-related pneumonia, severely impaired pulmonary function, etc. 16) Congenital or acquired immunodeficiency (e.g., HIV), or active hepatitis (liver

	enzymes not meeting inclusion criteria; for HBV: HBV DNA ≥10^4 copies/mL; for HCV: HCV RNA ≥10^3 copies/mL). Chronic HBV carriers with DNA ≥2000 IU/ml (≥10^4 copies/ml) can be enrolled only if antiviral therapy is administered during the study. 17) Concurrent participation in another clinical study or within 1 month of ending a previous study; likely to receive other systemic anti-tumor therapy during the study. 18) Known history of drug abuse, alcohol abuse, or drug addiction. 19) Inability or unwillingness to bear the cost of self-paid examinations/treatments. 20) Investigator judgment for exclusion due to other reasons potentially leading to study termination (e.g., other severe diseases including psychiatric, severe lab abnormalities, social/family factors affecting 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 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: September 2028

	Estimated study completion date: August 2033