Informed Consent Form

Subject Information Sheet

Protocol 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
Principal Investigators:
Sponsor: Tianjin Medical University Second Hospital

Dear Subject：

You are invited to participate in the clinical research study titled "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" This study is sponsored by The Second Hospital of Tianjin Medical University. Please read this informed consent form carefully and make a considered decision about whether to participate in this study. Your participation in this research is entirely voluntary. As a subject, you must provide your written consent before joining the clinical study. When your study doctor or research staff discusses this informed consent form with you, you can ask him/her to explain anything you do not understand. We encourage you to fully discuss your decision to participate with your family and friends. You have the right to refuse to participate in this study and may withdraw at any time without penalty or loss of benefits to which you are otherwise entitled. If you are currently participating in another study, please inform your study doctor or research staff. The background, purpose, research process, and other important information about this study are as follows:

1. Study Background

Upper Tract Urothelial Carcinoma (UTUC) is a highly aggressive malignant tumor. Radical Nephroureterectomy (RNU) is its standard treatment. However, even after surgery, the prognosis for patients with locally advanced disease remains poor. In this context, the value of concurrent Lymph Node Dissection (LND) has become the most controversial core issue in the field. Although current guidelines tend to recommend LND for high-risk UTUC patients, this recommendation lacks the highest level of evidence-based medical proof, leading to highly inconsistent clinical practice. There is an urgent need for a rigorous clinical trial to clarify its role.

The irreplaceable diagnostic value of LND is the basis for its application. Because

preoperative imaging has very low sensitivity for diagnosing lymph node metastasis, pathological examination is the only gold standard. Lymph node metastasis (pN+) is a recognized strong adverse prognostic factor, and indicators such as extranodal extension (ENE), lymphovascular invasion (LVI), and lymph node density (LNDensity) can more accurately predict the risk of recurrence and death. Accurate N staging is key to identifying high-risk patients for adjuvant therapy.

However, whether LND can directly improve survival by clearing micro-metastases —its therapeutic value—is currently supported by severely conflicting evidence. On one hand, numerous retrospective studies show that LND can significantly improve survival in high-risk (≥pT2) patients, and a higher lymph node yield (LN yield) is associated with better outcomes. On the other hand, several large multicenter studies, including the Japanese JCOG1110A and studies based on the US NCDB database, have failed to confirm that LND provides a survival benefit for patients.

This contradiction in evidence stems from the inherent limitations of previous studies. However, it is certain that we now have mature conditions for conducting high-quality clinical trials: including anatomy-based template dissection plans, safe and feasible minimally invasive surgical techniques, and uniform complication assessment standards. To resolve the controversy and provide decisive evidence for clinical practice, initiating a prospective randomized controlled trial is imperative. This study aims to definitively determine whether RNU combined with template LND, compared to RNU alone, can improve oncological outcomes safely in patients with non-metastatic UTUC. We believe the results of this study have the potential to revise clinical guidelines and ultimately improve the survival of UTUC patients worldwide.

2. Study Objectives

2.1 Primary Objectives：

1） To 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） To 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.

2.2 Secondary Objectives：

1） To 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）To establish a lymph node metastasis (pN+) map for UTUC at different sites in the high-risk UTUC population through template lymph node dissection.

2.3 Exploratory Objectives：

1）To utilize prospectively collected tumor tissues to explore molecular biomarkers for predicting prognosis through Bulk-RNA sequencing;

2）To 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.

3. Study Process

3.1 How many people will participate in this study?

Approximately 150 people will participate in this study conducted at Tianjin Medical University Second Hospital and other centers. Approximately [ ] people will participate in this study at our hospital.

3.2 Study Procedures

If you agree to participate in this study, please sign this informed consent form. This study includes three phases: the screening period, the treatment period, and the follow-up period.

1）Screening Period (From signing the informed consent form until before randomization, not exceeding 14 days)

You will need to sign this informed consent form. The study doctor will assess whether you fully meet the study's "Inclusion Criteria" and "Exclusion Criteria" through the following examinations:

Demographic data, medical history, physical examination, vital signs;

Performance status score (ECOG);

Laboratory tests: Complete blood count, urinalysis, blood biochemistry, coagulation function, thyroid function, cortisol + ACTH;

Virology tests: HIV, Hepatitis B, Hepatitis C;

Imaging examinations: Chest CT, abdominal contrast-enhanced CT/MRI, etc.;

For women of childbearing potential, a blood or urine pregnancy test is required.

2）Treatment Period (From randomization to 30 days postoperatively)

You will undergo surgical treatment according to the randomization result, assigned to

either Group A or Group B:

Group A (Experimental Intervention): Nephroureterectomy + Template Lymph Node Dissection

You will undergo nephroureterectomy, and the surgeon will perform lymph node dissection according to the protocol-defined template. The specific scope is as follows:

a) Renal Pelvis & Upper Ureter Tumors: Dissect renal hilum, para-aortic or para-caval lymph nodes (depending on affected side). Superior border: level of central adrenal vein (right) or superior border of adrenal gland; Inferior border: bifurcation of aorta or vena cava.

b) 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.

c) Lower Ureter Tumors: Dissect pelvic lymph nodes, including common iliac, external iliac, internal iliac, and obturator lymph node regions.

Group B (Control Intervention): Nephroureterectomy + Dissection of lymph nodes visible on imaging or intraoperatively (>1 cm)

You will undergo nephroureterectomy, and the surgeon will only remove suspicious lymph nodes larger than 1 cm in diameter found on preoperative imaging or during surgery.

The research team will record your perioperative data up to 30 days postoperatively.

3）Follow-up Period (Long-term Postoperative Follow-up)

a) Safety Follow-up:Track and record any adverse events until resolution, stabilization, or return to baseline levels.

b) 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.

c) Tumor Progression Follow-up:Starts postoperatively. Survival and recurrence data are collected via outpatient review and telephone follow-up. You need to undergo follow-up examinations on time to evaluate efficacy. According to the protocol:

Within 2 years postoperatively:Imaging (CT/MRI/US) and urinary cytology every 3 months, cystoscopy every 6 months.

Years 3-5 postoperatively:Follow-up intervals are extended to 6 months.

After 5 years:Annual review.

Follow-up will continue until you experience disease recurrence, death, loss to follow-up, withdrawal of consent, or the study ends (maximum follow-up 10 years).

3.3 Can I withdraw from this study midway?

You may choose to withdraw from the study at any time without losing any benefits to which you are entitled. However, if you decide to withdraw during the study, we encourage you to discuss it with your doctor first. If you experience a serious adverse event, or if your study doctor believes that continued participation is not in your best interest, he/she will decide to withdraw you from the study. The sponsor or regulatory authorities may also terminate the study during its course. Your withdrawal will not affect your normal medical care and rights.

If you withdraw from the study for any reason, you may be asked about your participation. If the doctor deems it necessary, you may also be required to undergo laboratory tests and physical examinations.

3.4. Information and Biological Specimens Collected in the Study

The information and biological samples (blood and tissue) collected after the study will be stored in Changyi Quan's department at our hospital and destroyed after 10 years. Your information or specimens may be used for future secondary data analysis.

4. Risks and Benefits

4.1. What are the risks of participating in this study?

1) Risks of Routine Surgery:Any nephroureterectomy carries inherent risks, including but not limited to: anesthesia accidents, bleeding, infection, pain, incision-related issues, and risks of injury to adjacent organs (such as intestines, spleen, pancreas, liver, major blood vessels, etc.).

2) Risks Related to the Experimental Group (Group A):As the "template lymph node dissection" has a wider surgical scope and is more complex, in addition to the above risks, you may face higher or additional risks:

a) Prolonged operative time and potentially increased intraoperative blood loss.

b) Lymphatic leakage/Chylous ascites:Injury to lymphatic vessels may lead to the accumulation of lymphatic fluid in the abdominal cavity, potentially requiring special diet, medication, or even surgical intervention.

c) Nerve injury:Nerves in the abdomen, such as the obturator nerve, may be damaged during dissection. In rare cases, this may affect ejaculatory function in males.

d) Vascular injury:The risk of injuring major blood vessels adjacent to the dissection area (such as the abdominal aorta, inferior vena cava, common/external/internal iliac arteries and their branches like the obturator artery, uterine artery; common/external/internal iliac veins and their tributaries like the obturator vein, presacral venous plexus) is theoretically increased.

e) Privacy breach risk:We will take strict measures to protect your personal

information, but there is a very small possibility of accidental disclosure during processing.

4.2. What are the benefits of participating in the study?

1) Direct Benefits:During this study, you will receive dedicated medical services from the study doctors and a surgical treatment plan following the guidelines for UTUC. The sponsor will waive the cost associated with the template lymph node dissection procedure during hospitalization, and the sponsor will also perform Bulk-RNA sequencing on your tumor tissue free of charge.

2) Potential Benefits:If you are assigned to the treatment group that is ultimately proven to be more effective, you may benefit directly. Furthermore, your contribution to this study will provide high-level evidence for the important medical question of "the optimal surgical approach for high-risk UTUC patients," potentially improving treatment outcomes for many future patients. Your participation will aid medical research and understanding of this disease, helping to improve future diagnosis and treatment levels. Here, we thank you for your willingness to participate in scientific research and contribute to the advancement of medicine!

5. Alternative Treatment Options

Apart from participating in this study, you could also receive conservative treatment. Please discuss these and other possible options with your doctor.

6. Use of Research Results and Confidentiality of Personal Information

With the understanding and assistance of you and other subjects, the results of this research project may be published in medical journals, but we will keep your research records confidential as required by law. The personal information of research subjects will be kept strictly confidential and will not be disclosed unless required by relevant laws. When necessary, government regulatory departments, the hospital ethics committee, and other relevant research personnel can access your information according to regulations.

7. Study Costs and Related Compensation

You will not need to pay for the investigational procedures specified in this study protocol that are beyond routine clinical practice. The costs of examinations, treatments, and medications that fall within the scope of routine diagnosis and treatment will still be borne by you or your medical insurance according to national and hospital regulations. As mentioned before, the sponsor will cover the cost of the template lymph node dissection

procedure. If injury directly related to this study occurs, the sponsor unit (Tianjin Medical University Second Hospital) will bear the corresponding medical expenses and provide economic compensation in accordance with relevant national laws and regulations.

8. Subject Rights and Relevant Precautions

8.1. Your Rights

Your participation throughout the study is voluntary. If you decide not to participate in this study, it will not affect any other treatment you should receive. If you decide to participate, you will be asked to sign this written informed consent form. You have the right to withdraw from the trial at any stage without discrimination or unfair treatment, and your corresponding medical treatment and rights will not be affected.

8.2. Precautions

As a subject, you need to provide truthful information about your medical history and current physical condition; inform the study doctor of any discomfort you experience during the study period; refrain from taking restricted medications, foods, etc., as instructed by the doctor; inform the study doctor if you have recently participated, or are currently participating, in other studies.(Precautions include the need for contraception, avoiding alcohol, avoiding combined traditional Chinese medicine treatment (unless prescribed by the investigator), etc. Required cooperation includes attention to special medication requirements, etc.)

9. Relevant Contact Information for Obtaining Information

If any significant new information arises during the research that may affect your willingness to continue participation, your doctor will notify you promptly. If you have questions about your research data, or if you wish to know the findings of this study after its completion, you can ask any questions related to this study at any time and receive corresponding answers. Please contact Changyi Quan and the team members at 022-88328607.

The study has been reviewed and approved by the Ethics Committee. If you have any questions related to your own rights/interests, or if you wish to report difficulties, dissatisfaction, or concerns encountered during your participation, or provide comments and suggestions related to this study, please contact the Ethics Committee of Tianjin Medical University Second Hosptial. Contact telephone: 022-88328108, Email: yd2y_llwyh@126.com.

Subject Signature Page

Informed Consent Statement:

I have been informed about the purpose, background, procedures, risks, and benefits of this research. I have had sufficient time and opportunity to ask questions, and the answers provided have satisfied me.

I have also been informed whom to contact if I have questions, wish to report difficulties, concerns, or suggestions regarding the study, or want to obtain further information or provide help for the research.

I have read this informed consent form and agree to participate in this study.

I understand that I can choose not to participate in this study or withdraw at any time during the study without giving any reason.

I understand that if my condition worsens, or if I experience a serious adverse event, or if my study doctor believes that continued participation is not in my best interest, he/she will decide to withdraw me from the study. The funding party or regulatory authorities may also terminate the study during its course without requiring my consent. If this occurs, the doctor will notify me promptly, and the study doctor will discuss my other options with me.

I will receive a copy of this informed consent form, containing the signatures of both myself and the investigator.

Subject Signature:_____ Date:_____

（Note: If the subject lacks capacity/has limited capacity, the legal representative must sign and date）

Subject Contact Information:_____

Legal Representative Signature:_____ Date:_____

（Note: If the subject cannot read this informed consent form, an independent witness is required to attest that the investigator has explained all contents of the informed consent form to the subject. The independent witness must sign and date）

Legal Representative Contact Information:_____

Independent Witness Signature:_____ Date:_____

Independent Witness Contact Information:_____

Investigator Signature_____ Date:_____

Investigator Contact Information:_____