Informed Consent Form

Subject Information Sheet

Protocol Title： Template Lymph Node Dissection for Tumor Control in High-Risk Renal Cell Carcinoma: A Prospective, Open-Label, Multicenter, Randomized Controlled Trial
Principal Investigators:
Sponsor: Tianjin Medical University Second Hospital

Dear Subject：
You are invited to participate in the clinical research study titled "Template Lymph Node Dissection for Tumor Control in High-Risk Renal Cell Carcinoma: A Prospective, Open-Label, Multicenter, Randomized Controlled Trial".This study is sponsored by The Second Hospital of Tianjin Medical University. Please read this informed consent form carefully and make a decision on 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 consent form with you, you can ask him/her to explain anything you do not understand. We encourage you to discuss fully with your family and friends before deciding to participate in this research. 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, procedures, and other important information of this study are provided below:

1. Study Background

The therapeutic value of lymph node dissection (LND) in renal cell carcinoma (RCC) remains a core controversy. Although LND has traditionally been considered a component of radical nephrectomy (RN), the only Phase III trial (EORTC 30881) showed no survival benefit in clinically node-negative (cN0) low-risk patients, leading current guidelines to restrict its application. However, this conclusion has limitations, as the nodal metastasis rate in that trial population was only 4.0%, making it impossible to evaluate the true value of LND in high-risk patients.

Retrospective studies suggest that in pathologically node-positive (pN+) patients, the thoroughness of LND (extent and number of nodes removed) is positively correlated with survival rates, especially in high-risk subgroups such as pT3-4 stage, tumor >10 cm, or sarcomatoid differentiation. LND is an independent protective factor for

cancer-specific survival, supporting the hypothesis that LND may directly alter the disease course by eliminating micro-metastases.

In clinical practice, imaging has low sensitivity (10-25%) for detecting metastases in normal-sized lymph nodes. In the era of immunotherapy, the survival benefit of adjuvant pembrolizumab highlights the importance of accurate staging (e.g., pN status). Previous retrospective data are from the pre-immunotherapy era and cannot distinguish between the direct therapeutic effect of LND and its staging/screening effect.

Therefore, this study targets high-risk populations with cT3-4 N0-1 M0 or post-treatment no evidence of disease (M1 NED), aiming to validate the independent therapeutic value of LND through a prospective randomized trial, filling the gap left by the EORTC 30881 trial and providing Level I evidence for surgical decision-making in high-risk RCC.

2. Study Objectives

2.1 Primary Objectives：

1） To compare the impact of nephrectomy combined with template lymph node dissection versus nephrectomy alone on Overall Survival (OS) and Disease-Free Survival (DFS) in high-risk RCC patients at risk for recurrence or progression;

2） To evaluate and compare the surgical safety between the two groups, including perioperative complications (graded by Clavien-Dindo classification), operation time, intraoperative blood loss, and hospital stay.

2.2 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.

2.3 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.

3. Study Process

3.1 How many people will participate in this study?

Approximately 220 people will participate in this study conducted at The Second Hospital of Tianjin Medical University and other centers. Approximately ( ) people will participate at this hospital.

3.2 Study Procedures

If you agree to participate, please sign this informed consent form. This study consists of three phases: Screening, Treatment, and Follow-up.

1）Screening Period (From signing the ICF until randomization, not exceeding 14 days)

You need to sign this ICF. The study doctor will assess whether you fully meet the study's Inclusion 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): Nephrectomy + Template Lymph Node Dissection

You will undergo radical nephrectomy, and the surgeon will perform a lymph node dissection according to the protocol-defined template. The specific ranges are:

Left Side: Lymphatic tissue anterior and lateral to the abdominal aorta from the diaphragmatic crus to the aortic bifurcation, including the hilar lymph nodes.

Right Side: 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.

Group B (Control Intervention): Nephrectomy + Resection of radiologically or

intraoperatively visible lymph nodes >1cm

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

The research team will record your perioperative data up to 30 days post-surgery. Regarding postoperative treatment: At the end of the treatment period, the investigator may recommend subsequent therapy. Based on your preference, you can choose whether to receive postoperative adjuvant therapy. If you agree to postoperative therapy and choose Toripalimab, the study will provide 4 cycles of the drug free of charge.

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

Safety Follow-up: Any adverse events will be tracked and recorded until resolution, stabilization, or return to baseline.

Tumor Progression Follow-up: You need to undergo regular reviews for efficacy assessment as per the protocol:

a)Within the first year after surgery: Imaging (CT/MRI) every 3 months.

b)Years 2-5 after surgery: Imaging every 6 months.

c)After 5 years: Imaging annually.

Follow-up will continue until disease recurrence, death, loss to follow-up, withdrawal of consent, or study end (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 otherwise 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 treatment and rights.

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

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) Conventional Surgical Risks: Any radical nephrectomy carries inherent risks, including but not limited to: anesthesia accidents, bleeding, infection, pain, incision-related issues, and risk of injury to adjacent organs (e.g., bowel, spleen, pancreas, liver, major blood vessels).

2) Risks related to the Experimental Group (Group A): As "Template Lymph Node Dissection" involves a wider surgical field and more complex procedures, in addition to the risks mentioned above, 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 medical services from a dedicated doctor and a surgical treatment plan following RCC diagnosis and treatment guidelines. The study sponsor will also cover the costs associated with the lymph node dissection procedure during your hospitalization. If you choose to receive adjuvant therapy postoperatively and use Toripalimab, the study sponsor will provide 1 cycles of the medication free of charge (the full postoperative treatment is 17 cycles, 1 cycle=21 days). The study will also perform Bulk-RNA sequencing on your tumor tissue free of charge.

2) Potential Benefits: You might benefit if you are assigned to the treatment group that ultimately proves to be more effective. Furthermore, your contribution to this study will provide high-level evidence for the important medical question of the "optimal surgical approach for high-risk RCC at risk of recurrence or progression," potentially improving treatment outcomes for many future patients. Your participation will also

contribute to further medical research and understanding of this disease, helping to improve future diagnosis and treatment levels. We thank you for your willingness to participate in scientific research and contribute to medical progress.

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 do not need to pay for the research 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, if you choose postoperative adjuvant therapy, the study sponsor will also provide 1 cycles of Toripalimab free of charge. If injury directly related to this research occurs, the sponsor unit (The Second Hospital of Tianjin Medical University) will bear the corresponding medical expenses and provide economic compensation according to 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:_____