


BMJ Open Preoperative stereotactic body radiotherapy combined with surgical treatment for renal cell carcinoma and inferior vena cava tumour thrombus: study protocol for a single-arm cohort trial

Yunchong Liu ,¹ Zhuo Liu,¹ Ran Peng,² Ruotao Xiao,¹ Junjie Wang,² Hao Wang,² Lulin Ma¹

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¹Department of Urology, Peking University Third Hospital, Beijing, China

²Department of Radiation Oncology, Peking University Third Hospital, Beijing, China

Correspondence to

Dr Lulin Ma;
malulinpk@163.com and
Dr Hao Wang;
hhbysy@126.com

ABSTRACT

Introduction Although surgery is currently the first choice for patients with renal cell carcinoma and vena cava tumour thrombus, the surgery is difficult, with many complications, and the prognosis of patients is not ideal. Renal cell carcinoma is not sensitive to traditional radiotherapy, but the development of stereotactic ablative body radiotherapy (SABR) technology with the characteristics of high precision, dose and conformity has made the radiotherapy of renal cell carcinoma reexamined.

Methods and analysis

Study design This trial is a single-arm cohort study sponsored by Peking University Third Hospital.

Study treatment Preoperative stereotactic ablative radiotherapy combined with surgical treatment.

Primary endpoints (1) Adverse reactions after 4–6 weeks of SABR. (2) Mayo staging of tumour thrombus. (3) The length of the tumour thrombus from the corresponding anatomical mark. (4) Invasion of the inferior vena cava wall. (5) Recurrent-free survival rate of the tumour. (6) Cancer-specific survival rate. (7) Overall survival rate. (8) Perioperative indicators including operation time, intraoperative bleeding volume and postoperative complications.

Secondary endpoints (1) The longest diameter of the tumour and (2) Lymph node condition.

Main inclusion criteria Patients with renal cell carcinoma and inferior vena cava tumour thrombus graded from Mayo II to IV and eligible for radical nephrectomy and inferior vena cava thrombectomy.

Main exclusion criteria Patients with previous targeted therapy, chemotherapy or other interventions, or who cannot tolerate SABR or surgery.

Planned sample size 20 patients.

Ethics and dissemination The trial protocol and the informed consent of the subjects were submitted and approved by the Peking University Biomedical Ethics Committee.

Trial registration number ChiCTR1800015118.

Strengths and limitations of this study

- The only preoperative radiotherapy study in Asia that focuses on tumour thrombus.
- A pioneering study on the prognostic value of pathological changes after radiotherapy.
- A single-arm study and no control group.
- Small sample size.

INTRODUCTION

Renal cell carcinoma (RCC) is a common malignant tumour of the urinary system and accounts for 2%–3% of adult malignant tumours.¹ Nearly one-third of the patients on presentation are locally advanced tumours (2010 American Joint Committee on Cancer (AJCC) renal cancer stage III or IV) at the time of diagnosis.² RCC has a tendency for venous invasion and 4%–10% of newly diagnosed cases have inferior vena cava tumour thrombus (IVCTT).³ Currently, the traditional treatment used for RCC combined with IVCTT is surgery. Commonly used surgical methods are open or laparoscopic radical nephrectomy +IVC thrombectomy,^{4 5} which have a high risk and require extremely proficient operating skills and surgical capabilities of the doctor.^{6–8} Open or laparoscopic surgery may have early postoperative complications, such as bleeding, lung infection, deep vein thrombosis of the lower limbs, pulmonary embolism, renal failure, liver failure, urinary fistula, chylous fistula and so on. Severe complications can even lead to death.³

At present, the main problems in the treatment of RCC combined with IVCTT can be summarised in the following aspects:

(1) The operation is with high difficulties, risks and many complications;³ (2) For Mayo I–IV grade, radical nephrectomy +IVC thrombectomy can improve the 5-year survival rate of patients, but it can only reach 40%–60%.⁹ How to further improve the survival rate of patients is a hot research topic and (3) When the tumour thrombus invades the inferior vena cava wall in a wide range, segmental resection of the inferior vena cava is required.¹⁰ Lower limb oedema and renal insufficiency may occur after surgery.

Nowadays, the equipment, technology and concept of radiotherapy have ushered in a leap-forward development. The development of intensity-modulated radiotherapy technology has allowed tumours and surrounding normal tissues to obtain completely different doses. Image-guided technology allows the doses given from the radiotherapy plan to hit the tumour accurately. Stereotactic ablative body radiotherapy (SABR) has greatly expanded and partially subverted the understanding of traditional radiobiology.¹¹ In the past 10 years, new explorations of renal cancer have been continuously reported, mainly confined to inoperable renal cancer patients, all using SABR technology, and its local control rate and survival rate have reached a high level.^{12–17} Many phase-II SABR clinical trials for RCC are ongoing (NCT02141919, NCT01890590, NCT02613819, NCT03747133 and NCT03108703). Combined with the good results achieved by the SABR technique in inoperable renal cancer patients, we expect that it can shrink and reduce the level of tumour thrombus, increase surgical resection rate and reduce surgical risk. Evidence has shown that SABR can reduce the transverse diameter of the tumour thrombus,¹⁸ which may help solve the problem of venous obstruction by tumour thrombus. And the team's long-term follow-up results of two cases showed that SABR to RCC with IVCTT could get good local tumour control in selected patients.¹⁹ Its safety and effectiveness need to be further examined.

Aims

To determine the safety of the treatment by the study of preoperative stereotactic radiotherapy combined with surgical treatment of patients with RCC and IVCTT. Main purpose: (1) To identify the acute and late toxicity of radiotherapy. Severe toxicity is defined as grade III–IV toxicity according to Common Terminology Criteria Adverse Events (CTCAE) V.4.0. 2. Secondary purpose: To identify whether the difficulty or risk of surgery is increased after radiotherapy by analysing perioperative complications, operation time, intraoperative bleeding volume, intraoperative transfusion volume of suspended red blood cells and postoperative hospital stay. Using the follow-up data of the patients to clarify the curative effect of the treatment: (1) For Mayo III–IV classification, it may reduce the difficulty of operation, blood loss, blood transfusion rate and perioperative complications; (2) For Mayo II–IV classification, preoperative radiotherapy+surgery may be better than surgery alone, which prolongs

survival and reduces recurrence rate and (3) When the tumour thrombus invades the inferior vena cava wall in a wide range, preoperative radiotherapy can be used to preserve the inferior vena cava vessel wall.

METHODS AND ANALYSIS

Study design

This trial is a single-arm cohort study. There is only one intervention group.

Inclusion criteria

1. Age \geq 18 years old.
2. Imaging examination of RCC with IVCTT.
3. IVCTT graded from Mayo II to Mayo IV.
4. Subjects eligible for SABR for IVC tumour thrombosis at the decision of the radiation oncologist.
5. Subjects eligible for radical nephrectomy and inferior vena cava thrombectomy at the decision of urologists.
6. ECOG 0–2.
7. Able to complete enhanced CT or enhanced MRI (either one) examination.

Exclusion criteria

1. Subjects with a history of radiotherapy in the area of RCC or IVCTT.
2. Subjects with a history of preoperative targeted therapy, preoperative chemotherapy or other related treatments.
3. Subjects with a history of pulmonary embolism.
4. Subjects with severe cardiopulmonary insufficiency, severe arrhythmia, myocardial infarction, angina pectoris, severe coagulation disease or severe liver disease that cannot tolerate SABR or surgery.
5. Subjects with diseases that severely affect the judgement of patients, such as mental disorders.

Endpoints

Primary endpoints

1. Adverse reactions after 4–6 weeks of SABR. Measurement time point: 4–6 weeks after SABR treatment. Measurement method: observation and inspection.
2. Mayo staging of tumour thrombus. Measurement time point: before and after radiotherapy. Measurement method: CT or MRI.
3. The length of the tumour thrombus from the corresponding anatomical mark. Measurement time point: before and after radiotherapy. Measurement method: CT or MRI.
4. Invasion of the inferior vena cava wall. Measurement time point: before and after radiotherapy. Measurement method: CT or MRI.
5. Recurrent-free survival rate of the tumour. Measurement time point: postoperative. Measurement method: CT or MRI, follow-up.
6. Cancer-specific survival rate. Measurement time point: postoperative. Measurement method: follow-up.

7. Overall survival rate. Measurement time point: postoperative. Measurement method: follow-up.
8. Perioperative indicators including operation time, intraoperative bleeding volume and postoperative complications. Measurement time point: postoperative. Measurement method: surgical record or observation and inspection.

Secondary endpoints

1. The longest diameter of the tumour. Measurement time point: before and after radiotherapy. Measurement method: CT or MRI.
2. Lymph node condition. Measurement time point: before and after radiotherapy. Measurement method: CT or MRI.

Statistical calculations for trial sample size

This study is based on the registered clinical trial study 'Neoadjuvant SABR for IVC Tumour Thrombus in Newly Diagnosed RCC'²⁰ retrieved on the Clinical trial website. It is a single-arm study and the sample size is 6 for lead-in phase and 23 for phase II. In our study, there is only one intervention group. The study will be conducted after the intervention. The focus is on the safety of the trial. The sample size is estimated to be 20 cases.

Treatment and follow-up

Twenty patients enrolled from outpatient service of Peking University Third Hospital in the intervention group are treated with preoperative SABR to assist surgery. A total radiation dose of 30 Gy with 5 fractions will be given to IVC of each patient.

Simulation before radiotherapy will start on day 1. The subject lies on his back with hands at his sides. The fixation technology of the negative pressure vacuum bag is used to fix his head, body and limbs simultaneously with a foot pedal. Using CT, MRI and PET-CT to scan the upper boundary of the tumour ≥ 15 cm upward, and the lower boundary ≥ 15 cm as the scanning range. CT images include unenhanced phase (as the reference image), arterial phase and venous phase with a slice thickness of 1–1.5 mm. MRI images include T1WI, T2WI, enhanced and DWI phases with a slice thickness of 1–3 mm. Target delineation will start on day 2. CT, MRI and PET-CT fusion will be performed, with CT unenhanced phase as the reference image to delineate the target area. Delineating vena cava tumour thrombus as gross tumour volume (GTV) and stomach, duodenum, jejunum, ileum, colon, spinal cord, liver, oesophagus as organs at risk. The planning target volume (PTV) is generated by adding a 3 mm margin around the GTV. On day 3, a prescription dose of PTV 30 Gy/5 Gy/6f over 1 week is designed by a senior medical physicist and approved by an expert. This prescription then will be uploaded to Accuray MultiPlan (Accuray, Sunnyvale, California, USA) treatment planning system. On day 4, cyberknife (CyberKnife VSI, Accuray) radiotherapy will be carried out following the radiotherapy plan after the treatment list signed and

confirmed by the radiotherapist in charge and the planning physicist. Two or more therapists will perform the radiotherapy. During the first treatment, the radiotherapist and physicist will jointly participate in the location verification.

After 4–6 weeks of rest, readmission to finish blood routine, blood biochemistry, coagulation function, urine routine, enhanced CT of the urinary system, enhanced MRI of inferior vena cava on readmission day 1. Complete preoperation preparations on readmission day 3. Radical nephrectomy + IVC thrombectomy will be performed on readmission day 4.

Postsurgery visits at 1, 2, 3, 7 days and the day leaving hospital and 3, 6, 9, 12 months after the date of radical nephrectomy and IVC thrombectomy include blood routine, blood biochemistry, erythrocyte sedimentation rate, coagulation function and urine routine.

Subjects will receive regular phone calls from the investigators to complete follow-up.

A SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) figure of detailed flow chart for minimum assessments during the treatment and follow-up phase is shown in [figure 1](#). A schematic outline of the treatment plan is shown in [figure 2](#).

Adverse events

Adverse events (AEs) for radiation and surgery will be collected, respectively.

SABR-related AEs are defined using CTCAE V.4.0. We are interested in acute and late toxicity including nausea, fatigue, anorexia, diarrhoea, enteritis, gastritis, fistula, dermatitis, anaemia, lymphopenia, neutropenia, thrombocytopenia and ALT/AST elevation. Severe toxicity is defined as grade III–IV toxicity according to CTCAE V.4.0.

Modified Clavien classification system²¹ is used to evaluate AEs in terms of surgery. Surgical AEs of interest are postoperative active bleeding, postoperative anaemia, wound infection, pulmonary infection, lower extremity deep vein thrombosis, pulmonary embolism, chylous fistula, renal dysfunction, hyperkalaemia and continuous venovenous haemodiafiltration.

If any serious AE or important AE occurs, regardless of whether it is related to the research intervention, or whether the intervention has been implemented, the investigator must be notified by telephone/fax within 24 hours of the occurrence.

Data analysis

The enumeration data are described by case number and percentage, and χ^2 test is used. Rank sum test is used to compare the rank data. The measurement data are expressed by means+SD. If the measurement data conform to normal distribution, independent sample t-test or analysis of variance is used. The Kaplan-Meier method will be used to calculate the tumour-free rate, tumour-specific survival rate, and overall survival rate with SPSS V.18.0 software, and the log-rank test will be performed. The comparability of data and the comparison of short-term

Stage	Outpatient screening stage	Preoperative radiotherapy stage	Post-radiotherapy monitoring stage	Surgical treatment stage	Follow-up stage			
					3 months after surgery	6 months after surgery	9 months after surgery	12 months after surgery
Timepoint	1 week	1 week	4-6 weeks after radiotherapy	1-2 weeks				
Visit	V0	V1	V2	V3	V4	V5	V6	V7
Study date (week)	Baseline	1	5-6	7-8	20	32	44	56
Physical examination	X	X	X	X	X	X	X	X
Laboratory tests	X	X	X	X	X	X	X	X
Imaging (CT/MRI)	X	X	X	X	X	X	X	X
Inclusion and exclusion	X							
Informed Consent	X							
Demographic data and medical history	X							
Adverse event (safety) monitoring		X	X	X	X	X	X	X
Effect monitoring		X	X	X	X	X	X	X

Figure 1 Flow chart for minimum assessments during treatment and follow-up phase.

efficacy before and after the test will be tested by Fisher's exact probability method. A $p < 0.05$ is considered statistically significant. Intention-to-treat analysis is used for the results of subjects who drop out, lost to follow-up or do not complete the trial process. Multiple imputation is used for missing data.

ETHICS AND DISSEMINATION

Ethics, informed consent and safety

The trial protocol and the informed consent of the subjects were submitted and approved by the Peking

University Biomedical Ethics Committee. The written informed consent form will be obtained from all individual participants in the study. The specific contents of the informed consent form are provided in online supplemental materials. If the protocol is revised, only the corresponding revised part and the revised informed consent form (if any) can be implemented after being reviewed and approved by the ethics committee, and a copy of the approval of the Peking University Biomedical Ethics Committee is required to be provided to the clinical monitor. If the revision of the protocol aims to

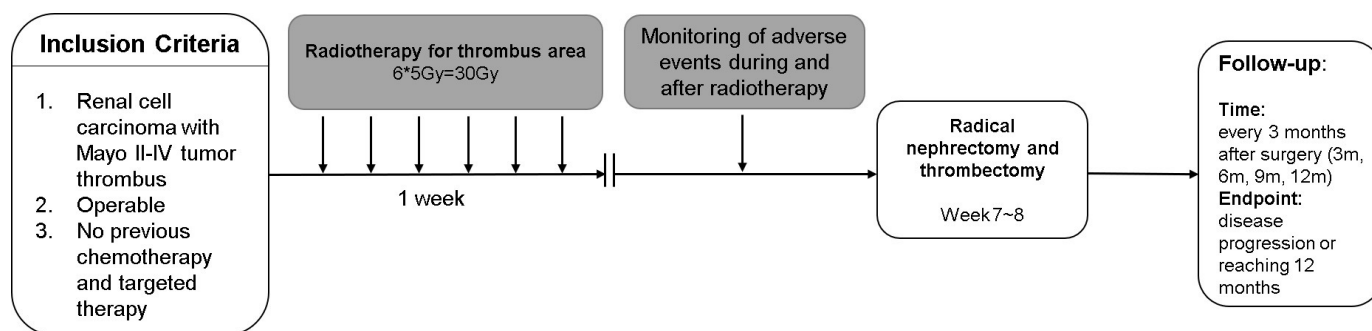


Figure 2 Schematic outline of the treatment plan. Patients with renal cell carcinoma with Mayo II-IV tumour thrombus will finish radiotherapy for thrombus area (total 30 Gy). Radical nephrectomy and thrombectomy will be performed between week 7 and 8. Follow-up for secondary endpoints will be starting at the date of nephrectomy and thrombectomy for 1 year every 3 months.

reduce the clear risk of the subjects, it can be implemented immediately, but it must be submitted to the relevant departments and the ethics committee for a record as soon as possible.

Confidentiality

The data involved in the research process will be taken care of to protect the privacy of the subjects. For example, the identification code table contains information such as the subject's name, phone number, identity number and home address. Researchers will keep it properly and take it out for inquiry when follow-up is needed. In addition, the cover and information page of case report form (CRF) will record the subject's initials rather than the signature of the name, and the informed consent signed by the subject will be kept separately from other information to prevent the disclosure of the subject's information.

Trial organisation

Our study is an investigator-initiated trial. The sponsor is Peking University, a Chinese government-funded university. This study is conducted in the urology ward and oncology radiotherapy ward of Peking University Third Hospital.

Data entry

According to the original observation records of the subjects, the researchers will load the data into the CRF timely, completely, correctly and clearly. The questionnaire reviewed and signed by the supervisor should be sent to the clinical research data administrator in time.

The corresponding database system will be used to input the data by two persons and two computers, and then the database will be compared twice. If any problem is found during the period, the inspector will be informed in time and the researcher will answer. The exchange of questions and answers should be in the form of question list, which should be kept for future reference.

Contents and methods of data verification and management

After all CRFs have been double-entered and verified, the data manager will write a database inspection report, which includes the completion of the study (including the list of dropped subjects), selection/exclusion criteria check, completeness check and logic consistency check, outlier data check, time window check, combined medication check, AE check, etc.

At the review meeting, the main researchers, monitors, data administrators and statisticians make decisions on the subjects' informed consent and issues raised in the database inspection report, and write a review report. The database will be locked at the same time.

To promote participant retention and complete follow-up, researchers should do a good job of subject compliance education during the process of informed consent and follow-up.

Data storage

After completing the data entry and verification as required, the CRF will be archived and stored in the order of numbers, and filled with a search catalogue for future reference. Electronic data files include databases, inspection procedures, analysis procedures, analysis results, codebooks and description files, etc, which will be stored in categories, and multiple backups will be stored on different disks or recording media, and they will be stored properly to prevent damage. All original archives will be kept within the corresponding period.

Protocol amendments

When the supervisors find that the phenomenon of non-compliance with the inclusion criteria persists, or the selection criteria are too strict, resulting in a low number of subjects, a supervision meeting will be carried out to amend the protocol.

Quality control

During the trial and research process, clinical monitors will be assigned to conduct regular on-site supervision visits to the research to ensure that all the contents of the research plan are strictly followed and the information filled in is correct. The process will be independent from investigators and the sponsor. The test centre shall objectively and truthfully record and retain all data and the execution and modification of the programme during the test and research process. During the recruitment phase, the consistency of the selection/exclusion criteria will be ensured as much as possible.

The specific supervision contents are as follows:

1. The research plan is submitted to the ethics committee for approval.
2. Participants in this study carefully implement the standard operating procedures for clinical verification before, during and after verification.
3. During the research process, the inspectors from the clinical trial research unit and the implementer monitor the correctness and completeness of the data in the CRF.
4. Researchers must undergo unified training, unified recording methods and judgement standards.
5. The investigator will fill in the CRF according to the requirements, truthfully, in detail, and carefully record the contents of the CRF to ensure that the content of the CRF is true and reliable.
6. All observations and findings in clinical research will be verified to ensure that the conclusions in the clinical verification are derived from the original data, and there are corresponding data management measures in the clinical verification and data processing.

Stopping guidelines

The principles and treatment methods for early termination of the study, including:

1. If serious safety problems are found in the trial, the clinical trial will be terminated in time.



2. The treatment effect of the experimental programme is too poor, or even ineffective, and has no clinical value.
3. There are major mistakes in the clinical trial protocol or serious deviations in the implementation, and it is difficult to evaluate the therapeutic effect.
4. The applicant requests to terminate the experiment or the administrative department requests to terminate the experiment.

DISCUSSION

This study aims to evaluate the safety of the treatment by the study of preoperative stereotactic radiotherapy combined with surgical treatment of patients with RCC and IVCTT.

Preoperative radiotherapy has been proven effective in many tumours, including rectal cancer, oesophageal cancer and soft-tissue sarcoma. Taking rectal cancer as an example, compared with surgery alone, the effects of preoperative radiotherapy are mainly reflected in (1) Reducing clinical staging and increasing surgical resection rate;²² (2) Increasing anus preservation rate and improving patients' quality of life²³ and (3) Reducing local recurrence rate and improving long-term survival rate.²⁴ However, the understanding of the effects of renal cancer radiotherapy has undergone a torturous process. In the past sixty years, the radiotherapy community has conducted high-quality randomised controlled studies, including preoperative radiotherapy, postoperative radiotherapy and intraoperative radiotherapy for renal cancer. Unfortunately, the conclusions of most studies show that radiotherapy does not improve the efficacy, and in some cases, it reduces the efficacy as well.^{25–27} Coupled with the later radiobiological studies suggesting that renal cancer is not sensitive to conventionally fractionated radiotherapy,²⁸ the research on renal cancer radiotherapy has fallen into a trough. In fact, in historical research, the backwardness of technology has led to insufficient doses. The prescribed doses given to tumours do not meet the standards for radical treatment.²⁹ At the same time, normal tissues are not well protected, including the duodenum and liver, which have been exposed to excessive radiation.

SABR, also known as stereotactic body radiotherapy, uses high-precision radiotherapy technology to focus the radical radiation dose (single dose >8–10 Gy) to the tumour site through external irradiation to achieve the purpose of radical treatment of the tumour. It has the characteristics of high precision, high dose, high conformability and low treatment frequency. It has been gradually used in the treatment of solid tumours such as liver cancer, lung cancer and spinal tumours in recent years, with definite curative effect.³⁰ SABR was first clinically applied for stage I non-small cell lung carcinoma, and related literature reports that the long-term local tumour control rate can reach 90%.³¹

In the existing researches on the treatment of RCC with SABR, the separated fractions and radiation doses are different. A study¹⁶ found that the SABR regimen with four fractions and a total radiation dose of 48 Gy has no significant dose-related adverse reactions, which is safe and feasible for patients with localised RCC. Another study¹³ recommended using five fractions and a total radiation dose of 35 Gy to treat patients with inoperable metastatic renal cancer. The existing lead-in trial results of SABR for RCC with IVCTT with a dose of 40 Gy in 5 fractions has shown safety.³² Most SABR protocols often use 3–5 fractions.^{33 34} We choose tumour thrombus as the target organ of radiotherapy, not including renal cancer tissue, to avoid the difficulty of surgical separation of the kidney due to oedema, fibrosis or other reasons after irradiation. Since the growth level of the tumour thrombus usually coincides with the horizontal part of the duodenum, the duodenal perforation will happen if the radical dose of the tumour thrombus is taken. Based on the results of existing studies and to limit organ toxicity, our trial design adopts a more conservative total radiation dose —30 Gy with five fractions.

Whether preoperative radiotherapy will increase the difficulty of the surgery is another important issue. Existing research shows that preoperative radiotherapy for rectal cancer does not increase the difficulty of operation and the incidence of postoperative complications.³⁵ Based on this, we believe that a reasonable neoadjuvant radiotherapy scheme will not increase the operation difficulty of RCC and inferior vena cava tumour. Considering that the hyperaemia and oedema^{36 37} of tumour-adjacent tissues in a short time after radiotherapy may increase the risk of surgery, we decide to operate 6–8 weeks after radiotherapy. At that time, the peritumoural oedema will be reduced, and the tumour will not continue to grow due to too long delay.

The clinical significances of this trial are as follows: (1) For Mayo III–IV classification, it may reduce the difficulty of operation, blood loss, blood transfusion rate and perioperative complications. Some cases of Mayo IV grade may require cardiac surgery interventions for complete surgical treatment,³⁸ and preoperative radiotherapy may create the possibility of not needing cardiac surgery; (2) For Mayo II–IV classification, preoperative radiotherapy+surgery may be better than surgery alone, which prolongs survival and reduces recurrence rate and (3) When the tumour thrombus invades the inferior vena cava wall in a wide range, preoperative radiotherapy can be used to preserve the inferior vena cava vessel wall.

The pathological changes of tumours after radiotherapy have been proved to have prognostic significance in other tumours.^{22 39} Tumours such as rectal cancer have clear grading standards, which are divided into four grades according to the degree of residual tumour after radiotherapy. Different grades correspond to different prognoses. So far, this study is the only preoperative radiotherapy study in the world that focuses on tumour thrombus, and is also a pioneering study on the

prognostic value of pathological changes after radiotherapy. Therefore, this study attempts to initially explore the postradiotherapy changes of renal tumour thrombus, and judge the prognosis of the tumour according to the different pathological changes.

We hope to collect possible treatment data for a further large trial by this study.

Trial status

Protocol version number: 2018-04-17. V.2.30.

Recruitment began on 1 May 2018 and will be completed in March 2022.

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Contributors Project development: ZL, RP, JW, HW and LM; Wrote study protocol: YL, ZL, RP and RX; Wrote this manuscript: YL, ZL and RP. All authors have read and approved this manuscript and ensured that this is the case.

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ORCID iD

Yunchong Liu <http://orcid.org/0000-0002-8851-457X>

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