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

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## Abstract

**Introduction:** Although surgery is currently the first choice for patients with renal cell carcinoma and vena cava tumor 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 endpoint:** (1) Adverse reactions after 4-6 weeks of SABR. (2) Perioperative indicators including operation time, intraoperative bleeding volume, and postoperative complications.

**Secondary endpoint:** (1) Mayo staging of tumor thrombus. (2) The length of the tumor thrombus from the corresponding anatomical mark. (3) Invasion of the inferior vena cava wall. (4) The longest diameter of the tumor. (5) Lymph node condition. (6) Recurrent-free survival (RFS) rate of the tumor. (7) Cancer-specific survival rate. (8) Overall survival rate.

**Main inclusion criteria:** Patients with renal cell carcinoma and inferior vena cava tumor 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:** ChiCTR1800015118. Clinical trials on the safety and effectiveness of neoadjuvant stereotactic radiotherapy combined with surgical treatment for patients with renal cell carcinoma with inferior vena cava tumor thrombus. Registered 08 March 2018, http://www.chictr.org.cn/showproj.aspx?proj=25747

**Keywords:** stereotactic ablative radiotherapy, renal cell carcinoma, inferior vena cava tumor thrombus, preoperative, safety

**Strengths and limitations of this study**

Strengths

- The only preoperative radiotherapy study in the world that focuses on tumor thrombus
- A pioneering study on the prognostic value of pathological changes after radiotherapy

limitations

- A single-arm study and no control group
- Small sample size

# Introduction

Renal cell carcinoma (RCC) is a common malignant tumor of the urinary system and accounts for 2~3% of adult malignant tumors[1]. Nearly 1/3 of the patients on presentation are locally advanced tumors (2010 AJCC renal cancer stage III or IV) at the time of diagnosis[2]. RCC has a tendency for venous invasion and 4% to 10% of newly diagnosed cases have inferior vena cava tumor 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. 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 summarized 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%[6]. How to further improve the survival rate of patients is a hot research topic. ③ When the tumor thrombus invades the inferior vena cava wall in a wide range, segmental resection of the inferior vena cava is required[7]. Lower limb edema 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 tumors and surrounding normal tissues to obtain completely different doses. Image-guided technology allows the doses given from the radiotherapy plan to hit the tumor accurately. Stereotactic ablative body radiotherapy (SABR) has greatly expanded and partially subverted the understanding of traditional radiobiology. 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[8-13].

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 tumor thrombus, increase surgical resection rate, and reduce surgical risk. Up till now, there is only one case report[14] about SABR for renal cell carcinoma with tumor thrombus. 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 renal cell carcinoma and inferior vena cava tumor thrombus. 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) v4.0. 2.To identify whether the difficulty or risk of surgery is increased after radiotherapy by analyzing perioperative complications, operation time, intraoperative bleeding volume, intraoperative transfusion volume of suspended red blood cells, and postoperative hospital stay. Secondary purpose: 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. 3. When the tumor 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 ≥ 18 years old.

(2) Imaging examination of renal cell carcinoma with inferior vena cava tumor thrombus.

(3) Inferior vena cava tumor thrombus graded from Mayo II to Mayo IV.

(4) Oncologists believe that patients are suitable for preoperative stereotactic ablative body radiotherapy (SABR) to treat inferior vena cava tumor thrombus.

(5) Urologists believe that patients are suitable for radical nephrectomy and inferior vena cava thrombectomy to treat renal cancer and inferior vena cava tumor thrombus.

(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 renal cell carcinoma or inferior vena cava tumor thrombus.

(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 judgment 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) 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) Mayo staging of tumor thrombus. Measurement time point: before and after radiotherapy. Measurement method: CT or MRI.

(2) The length of the tumor thrombus from the corresponding anatomical mark. Measurement time point: before and after radiotherapy. Measurement method: CT or MRI.

(3) Invasion of the inferior vena cava wall. Measurement time point: before and after radiotherapy. Measurement method: CT or MRI.

(4) The longest diameter of the tumor. Measurement time point: before and after radiotherapy. Measurement method: CT or MRI.

(5) Lymph node condition. Measurement time point: before and after radiotherapy. Measurement method: CT or MRI.

(6) Recurrent-free survival (RFS) rate of the tumor. Measurement time point: postoperative. Measurement method: CT or MRI, follow-up.

(7) Cancer-specific survival rate. Measurement time point: postoperative. Measurement method: follow-up.

(8) Overall survival rate. Measurement time point: postoperative. Measurement method: follow-up.

**Statistical calculations for trial sample size**

This study is based on the registered clinical trial study "Neo-adjuvant SABR for IVC Tumor Thrombus in Newly Diagnosed RCC"[15] retrieved on the Clinical trial website. The study sample size is two groups with 15 cases in each group. 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**

20 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 utilized 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 tumor ≥15cm upward, and the lower boundary ≥15cm as the scanning range. CT images include unenhanced phase (as the reference image), arterial phase, and venous phase with a slice thickness of 1-1.5mm. MRI images include T1WI, T2WI, enhanced and DWI phases with a slice thickness of 1-3mm. 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 tumor thrombus as gross tumor volume (GTV) and stomach, duodenum, jejunum, ileum, colon, spinal cord, liver, esophagus as organs at risk (OAR). The planning target volume (PTV) is generated by adding a 3mm margin around the GTV. On day 3, a prescription dose of PTV 30Gy/5Gy/6f is designed by a senior medical physicist and approved by an expert. This prescription then will be uploaded to Accuray MultiPlan® (Accuray Inc., Sunnyvale, CA) treatment planning system. On day 4, cyberknife (CyberKnife ® VSI™, Accuray Inc., Sunnyvale, CA) 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, re-admission to finish blood routine, blood biochemistry, coagulation function, urine routine, enhanced CT of the urinary system, enhanced MRI of inferior vena cava on re-admission day 1. Complete pre-operation preparations on re-admission day 3. Radical nephrectomy + IVC thrombectomy will be performed on re-admission day 4.

Post-surgery 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 figure of detailed flowchart 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 Common Terminology Criteria for Adverse Events (CTCAE) v4.0. We are interested in acute and late toxicity including nausea, fatigue, anorexia, diarrhea, enteritis, gastritis, fistula, dermatitis, anemia, lymphopenia, neutropenia, thrombocytopenia, and ALT/AST elevation. Severe toxicity is defined as grade III-IV toxicity according to CTCAE v4.0.

Modified Clavien classification system[16] is used to evaluate adverse events in terms of surgery. Surgical AEs of interest are postoperative active bleeding, postoperative anemia, wound infection, pulmonary infection, lower extremity deep vein thrombosis, pulmonary embolism, chylous fistula, renal dysfunction, hyperkalemia, and continuous venovenous hemodiafiltration.

If any serious adverse event or important adverse event 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 chi square test is used. Rank sum test is used to compare the rank data. The measurement data are expressed by means + standard deviation. 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 tumor-free rate, tumor-specific survival rate, and overall survival rate with SPSS 18.0 software, and the Log-rank test will be performed. The comparability of data and the comparison of short-term efficacy before and after the

test will be tested by Fisher's exact probability method. 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 the supplementary 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 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, ID 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 organization

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 case report form 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 case report forms 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, adverse event 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 case report form will be archived and stored in the order of numbers, and filled with a search catalog 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 center shall objectively and truthfully record and retain all data and the execution and modification of the program 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 judgment standards.

(5) The investigator will fill in the case report form according to the requirements, truthfully, in detail, and carefully record the contents of the CRF to ensure that the content of the case report form 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 program 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 renal cell carcinoma and inferior vena cava tumor thrombus.

Preoperative radiotherapy has been proven effective in many tumors, including rectal cancer, esophageal cancer, and soft tissue sarcoma. Taking rectal cancer as an example, compared with surgery alone, the effects of preoperative radiotherapy are mainly reflected in ①Reducing clinical staging and increasing surgical resection rate[17]. ②Increasing anus preservation rate and improving patients' quality of life[18]. ③Reducing local recurrence rate and improving long-term survival rate[19]. 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 randomized 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[20-22]. Coupled with the later radiobiological studies suggesting that renal cancer is not sensitive to conventionally fractionated radiotherapy[23], 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 tumors do not meet the standards for radical treatment[24]. 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 (SBRT), uses high-precision radiotherapy technology to focus the radical radiation dose (single dose> 8-10 Gy) to the tumor site through external irradiation to achieve the purpose of radical treatment of the tumor. 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 tumors such as liver cancer, lung cancer, and spinal tumors in recent years, with definite curative effect[25]. SABR was firstly clinically applied for stage I non-small cell lung carcinoma, and related literature reports that the long-term local tumor control rate can reach 90%[26].

In the existing researches on the treatment of renal cell carcinoma with SABR, the separated fractions and radiation doses are different. A study[12] found that the SABR regimen with 4 fractions and a total radiation dose of 48 Gy has no significant dose-related adverse reactions, which is safe and feasible for patients with localized renal cell carcinoma. Another study[9] recommended using 5 fractions and a total radiation dose of 35Gy to treat patients with inoperable metastatic renal cancer. Most SABR protocols often use 3 to 5 fractions[27,28]. We choose tumor thrombus as the target organ of radiotherapy, not including renal cancer tissue, to avoid the difficulty of surgical separation of the kidney due to edema, fibrosis, or other reasons after irradiation. Since the growth level of the tumor thrombus usually coincides with the horizontal part of the duodenum, the duodenal perforation will happen if the radical dose of the tumor 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 - 30Gy with 5 fractions.

Considering that the hyperemia and edema[29,30] of tumor-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 peritumoral edema will be reduced, and the tumor will not continue to grow due to too

long delay.

The clinical significances of this trial are as follows: ①For Mayo III-IV classification, it may reduce the difficulty of operation, blood loss, blood transfusion rate, and perioperative complications. ②For Mayo II-IV classification, preoperative radiotherapy + surgery may be better than surgery alone, which prolongs survival and reduces recurrence rate. ③When the tumor 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 tumors after radiotherapy have been proved to have prognostic significance in other tumors[17,31]. Tumors such as rectal cancer have clear grading standards, which are divided into 4 grades according to the degree of residual tumor after radiotherapy. Different grades correspond to different prognoses. So far, this study is the only preoperative radiotherapy study in the world that focuses on tumor thrombus, and is also a pioneering study on the prognostic value of pathological changes after radiotherapy. Therefore, this study attempts to initially explore the post-radiotherapy changes of renal tumor thrombus, and judge the prognosis of the tumor 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. V2.30.

Recruitment began on 2018-05-01 and will be completed in 2021-12.

**Abbreviations**

AEs: adverse events; CRF: case report form; CTCAE: Common Terminology Criteria Adverse Events; ECOG: Eastern Cooperative Oncology Group; GTV: gross tumor volume; IVCTT: inferior vena cava tumor thrombus; OAR: organs at risk; PTV: planning target volume; RCC: Renal cell carcinoma; RFS: Recurrent-free survival; SABR: stereotactic ablative body radiotherapy; SBRT: stereotactic body radiotherapy

# Declarations

## Patient and Public Involvement

Patients or the public will not be involved in the design, or conduct, or reporting, or dissemination plans of our research.

## Consent for publication

Not applicable.

## Availability of data and materials

Researchers, monitors and reviewers of ethics committees will have access to the final trial dataset.

## Dissemination policy

Investigators and sponsor will communicate trial results to participants, healthcare professionals, the public, and other relevant groups via publication. The public will access to the full protocol, participant-level dataset, and statistical code from online database. Professional medical writers will complete an article of this trial.

## Authors' contributions

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

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## Competing interests statement

The authors declare that they have no competing interests.

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| Timepoint | 1 week | 1 week | 4-6 weeks after radiotherapy | 1-2 weeks | 3 months after surgery | 6 months after surgery | 9 months after surgery | 12 months after surgery |
|---|---|---|---|---|---|---|---|---|
| Study date（week） | Baseline | 1 | 5-6 | 7-8 | 20 | 32 | 44 | 56 |
| Laboratory tests | X | X | X | X | X | X | X | X |
| Inclusion and exclusion | X | | | | | | | |
| Demographic data and medical history | X | | | | | | | |
| Effect monitoring | | X | X | X | X | X | X | X |

Figure 1. Flowchart for minimum assessments during treatment and follow up phase

215x173mm (150 x 150 DPI)

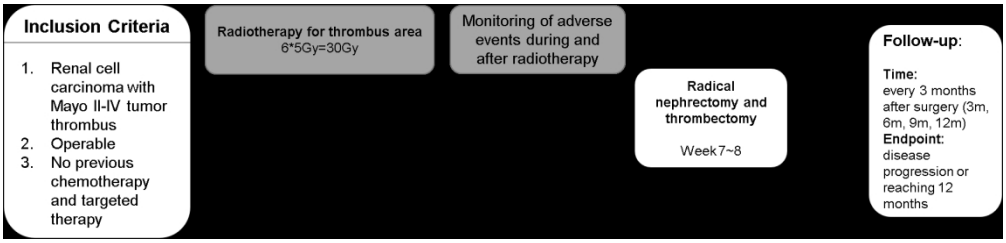


Figure 2. Schematic outline of the treatment plan. Patients with renal cell carcinoma with Mayo II-IV tumor thrombus will finish radiotherapy for thrombus area (total 30Gy). Radical nephrectomy and thrombectomy will be performed between week 7~8. Follow up for secondary endpoints will be starting at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

314x73mm (150 x 150 DPI)

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description |
|---|---|---|
| **Administrative information** | | |
| Title | 1 | Title. |
| Trial registration | 2a | Line 29-32 |
| | 2b | N/A. This trial was registered on Chinese Clinical Trial Registry. |
| Protocol version | 3 | Line 328 |
| Funding | 4 | Line 353-356 |
| Roles and responsibilities | 5a | Line 1-5 & 349-352 |
| | 5b | Line 6 |
| | 5c | Line 349-352 |
| | 5d | Line 242-261 |
| **Introduction** | | |
| Background and rationale | 6a | Line 42-71 |
| | 6b | N/A. This is not a controlled trial and comparator is not applicable. |
| Objectives | 7 | Line 72-85 |
| Trial design | 8 | Line 88 |
| **Methods: Participants, interventions, and outcomes** | | |
| Study setting | 9 | Line 209-212 |
| Eligibility criteria | 10 | Line 89-107 |
| Interventions | 11a | Line 137-167 |
| | 11b | N/A. Not covered in our trial. |
| | 11c | N/A. Not covered in our trial. |

| | | |
|---|---|---|
| | 11d | N/A. Not covered in our trial. |
| Outcomes | 12 | Line 109-130 |
| Participant timeline | 13 | Figure 1&2. |
| Sample size | 14 | Line 131-136 |
| Recruitment | 15 | Line 138-140 |
| **Methods: Assignment of interventions (for controlled trials)** | | |
| Allocation: | | |
| Sequence generation | 16a | N/A. This is not a controlled trial. |
| Allocation concealment mechanism | 16b | N/A. This is not a controlled trial. |
| Implementation | 16c | N/A. This is not a controlled trial. |
| Blinding (masking) | 17a | N/A. This is not a controlled trial. |
| | 17b | N/A. This is not a controlled trial. |
| **Methods: Data collection, management, and analysis** | | |
| Data collection methods | 18a | Line 213-228 |
| | 18b | Line 229-230 |
| Data management | 19 | Line 231-237 |
| Statistical methods | 20a | Line 182-188 |
| | 20b | N/A. There are no additional analyses due to small sample size. |
| | 20c | Line 189-190 |
| **Methods: Monitoring** | | |
| Data monitoring | 21a | Line 242-261 |
| | 21b | Line 262-270 |
| Harms | 22 | Line 168-180 |
| Auditing | 23 | Line 243-246 |
| **Ethics and dissemination** | | |

| | | |
|---|---|---|
| Research ethics approval | 24 | Line 192-201 |
| Protocol amendments | 25 | Line 238-241 |
| Consent or assent | 26a | Line 193-196 |
| | 26b | N/A. Participant data and biological specimens will not be used in ancillary studies. |
| Confidentiality | 27 | Line 202-208 |
| Declaration of interests | 28 | Line 358 |
| Access to data | 29 | Line 343 |
| Ancillary and post-trial care | 30 | N/A. There is no compensation to those who suffer harm from trial participation except medical care. |
| Dissemination policy | 31a | Line 345-348 |
| | 31b | Line 345-348 |
| | 31c | Line 345-348 |
| **Appendices** | | |
| Informed consent materials | 32 | Line 193-196 |
| Biological specimens | 33 | N/A. No biological specimens will be used for genetic or molecular analysis. |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

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

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| Primary Subject Heading: | Urology |
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| | |

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

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## Abstract

**Introduction:** Although surgery is currently the first choice for patients with renal cell carcinoma and vena cava tumor 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 endpoint:** (1) Adverse reactions after 4-6 weeks of SABR and after operation.

**Secondary endpoints:** (1) Perioperative indicators including operation time, intraoperative bleeding

volume, and postoperative complications. (2) Mayo staging of tumor thrombus. (3) The length of the tumor thrombus from the corresponding anatomical mark. (4) Invasion of the inferior vena cava wall. (5) The longest diameter of the tumor. (6) Lymph node condition. (7) Recurrent-free survival (RFS) rate of the tumor. (8) Cancer-specific survival rate. (9) Overall survival rate.

**Main inclusion criteria:** Patients with renal cell carcinoma and inferior vena cava tumor 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:** ChiCTR1800015118. Clinical trials on the safety and effectiveness of neoadjuvant stereotactic radiotherapy combined with surgical treatment for patients with renal cell carcinoma with inferior vena cava tumor thrombus. Registered 08 March 2018, http://www.chictr.org.cn/showproj.aspx?proj=25747

**Keywords:** stereotactic ablative radiotherapy, renal cell carcinoma, inferior vena cava tumor thrombus, preoperative, safety

**Strengths and limitations of this study**

Strengths

- The only preoperative radiotherapy study in Asia that focuses on tumor thrombus
- A pioneering study on the prognostic value of pathological changes after radiotherapy

limitations

- A single-arm study and no control group
- Small sample size

# Introduction

Renal cell carcinoma (RCC) is a common malignant tumor of the urinary system and accounts for 2~3% of adult malignant tumors[1]. Nearly 1/3 of the patients on presentation are locally advanced tumors (2010 AJCC renal cancer stage III or IV) at the time of diagnosis[2]. RCC has a tendency for venous invasion and 4% to 10% of newly diagnosed cases have inferior vena cava tumor 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 summarized 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. ③ When the tumor thrombus invades the inferior vena cava wall in a wide range, segmental resection of the inferior vena cava is required[10]. Lower limb edema 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 tumors and surrounding normal tissues to obtain completely different doses. Image-guided technology allows the doses given from the radiotherapy plan to hit the tumor 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 renal cell carcinoma 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 tumor thrombus, increase surgical resection rate, and reduce surgical risk. Evidence has shown that SABR can reduce the transverse diameter of the tumor thrombus[18], which may help solve the problem of venous obstruction by tumor thrombus. And the team's long-term follow-up results of two cases showed that SABR to RCC with IVCTT could get good local tumor 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 renal cell carcinoma and inferior vena cava tumor thrombus. 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) v4.0. 2. Secondary purpose: To identify whether the difficulty or risk of surgery is increased after radiotherapy by analyzing 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. 3. When the tumor 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 ≥ 18 years old.

(2) Imaging examination of renal cell carcinoma with inferior vena cava tumor thrombus.

(3) Inferior vena cava tumor thrombus graded from Mayo II to Mayo IV.

(4) Subjects eligible for SABR for IVC tumor 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 renal cell carcinoma or inferior vena cava tumor thrombus.

(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 judgment of patients, such as mental disorders.

## Endpoints

***Primary endpoint***

(1) Adverse reactions after 4-6 weeks of SABR and after operation. Measurement time point: 4-6 weeks after SABR treatment and after operation. Measurement method: observation and inspection.

***Secondary endpoints***

(1) Perioperative indicators including operation time, intraoperative bleeding volume, and postoperative complications. Measurement time point: postoperative. Measurement method: surgical record or observation and inspection.

(2) Mayo staging of tumor thrombus. Measurement time point: before and after radiotherapy. Measurement method: CT or MRI.

(3) The length of the tumor 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) The longest diameter of the tumor. Measurement time point: before and after radiotherapy. Measurement method: CT or MRI.

(6) Lymph node condition. Measurement time point: before and after radiotherapy. Measurement method: CT or MRI.

(7) Recurrent-free survival (RFS) rate of the tumor. Measurement time point: postoperative. Measurement method: CT or MRI, follow-up.

(8) Cancer-specific survival rate. Measurement time point: postoperative. Measurement method: follow-up.

(9) Overall survival rate. Measurement time point: postoperative. Measurement method: follow-up.

**Statistical calculations for trial sample size**

This study is based on the registered clinical trial study "Neo-adjuvant SABR for IVC Tumor Thrombus in Newly Diagnosed RCC"[20] retrieved on the Clinical trial website. It's 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**

20 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 utilized 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 tumor ≥15cm upward, and the lower boundary ≥15cm as the scanning range. CT images include unenhanced phase (as the reference image), arterial phase, and venous phase with a slice thickness of 1-1.5mm. MRI images include T1WI, T2WI, enhanced and DWI phases with a slice thickness of 1-3mm. 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 tumor thrombus as gross tumor volume (GTV) and stomach, duodenum, jejunum, ileum, colon, spinal cord, liver, esophagus as organs at risk (OAR). The planning target volume (PTV) is generated by adding a 3mm margin around the GTV. On day 3, a prescription dose of PTV 30Gy/5Gy/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 Inc., Sunnyvale, CA) treatment planning system. On day 4, cyberknife (CyberKnife ® VSI™, Accuray Inc., Sunnyvale, CA) 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, re-admission to finish blood routine, blood biochemistry, coagulation function, urine routine, enhanced CT of the urinary system, enhanced MRI of inferior vena cava on re-admission day 1. Complete pre-operation preparations on re-admission day 3. Radical nephrectomy + IVC thrombectomy will be performed on re-admission day 4.

Post-surgery 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 figure of detailed flowchart 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 Common Terminology Criteria for Adverse Events (CTCAE) v4.0. We are interested in acute and late toxicity including nausea, fatigue, anorexia, diarrhea, enteritis, gastritis, fistula, dermatitis, anemia, lymphopenia, neutropenia, thrombocytopenia, and ALT/AST elevation. Severe toxicity is defined as grade III-IV toxicity according to CTCAE v4.0.

Modified Clavien classification system[21] is used to evaluate adverse events in terms of surgery. Surgical AEs of interest are postoperative active bleeding, postoperative anemia, wound infection, pulmonary infection, lower extremity deep vein thrombosis, pulmonary embolism, chylous fistula, renal dysfunction, hyperkalemia, and continuous venovenous hemodiafiltration.

If any serious adverse event or important adverse event 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 chi square test is used. Rank sum test is used to compare the rank data. The measurement data are expressed by means + standard deviation. 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 tumor-free rate, tumor-specific survival rate, and overall survival rate with SPSS 18.0 software, and the Log-rank test will be performed. The comparability of data and the comparison of short-term efficacy before and after the test will be tested by Fisher's exact probability method. $P<0.05$ 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 the supplementary 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 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, ID 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 organization**

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 case report form 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 case report forms 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, adverse event 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 case report form will be archived and stored in the order of numbers, and filled with a search catalog 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 center shall objectively and truthfully record and retain all data and the execution and modification of the program 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 judgment standards.

(5) The investigator will fill in the case report form according to the requirements, truthfully, in detail, and carefully record the contents of the CRF to ensure that the content of the case report form 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 program 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 renal cell carcinoma and inferior vena cava tumor thrombus.

Preoperative radiotherapy has been proven effective in many tumors, including rectal cancer,

esophageal cancer, and soft tissue sarcoma. Taking rectal cancer as an example, compared with surgery alone, the effects of preoperative radiotherapy are mainly reflected in ①Reducing clinical staging and increasing surgical resection rate[22]. ② Increasing anus preservation rate and improving patients' quality of life[23]. ③Reducing 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 randomized 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 tumors 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 (SBRT), uses high-precision radiotherapy technology to focus the radical radiation dose (single dose> 8-10 Gy) to the tumor site through external irradiation to achieve the purpose of radical treatment of the tumor. 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 tumors such as liver cancer, lung cancer, and spinal tumors in recent years, with definite curative effect[30]. SABR was firstly clinically applied for stage I non-small cell lung carcinoma, and related literature reports that the long-term local tumor control rate can reach 90%[31].

In the existing researches on the treatment of renal cell carcinoma with SABR, the separated fractions and radiation doses are different. A study[16] found that the SABR regimen with 4 fractions and a total radiation dose of 48 Gy has no significant dose-related adverse reactions, which is safe and feasible for patients with localized renal cell carcinoma. Another study[13] recommended using 5 fractions and a total radiation dose of 35Gy to treat patients with inoperable metastatic renal cancer. The existing lead-in

trial results of SABR for RCC with IVCTT with a dose of 40Gy in 5 fractions has shown safety[32]. Most SABR protocols often use 3 to 5 fractions[33,34]. We choose tumor thrombus as the target organ of radiotherapy, not including renal cancer tissue, to avoid the difficulty of surgical separation of the kidney due to edema, fibrosis, or other reasons after irradiation. Since the growth level of the tumor thrombus usually coincides with the horizontal part of the duodenum, the duodenal perforation will happen if the radical dose of the tumor 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 - 30Gy with 5 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 renal cell carcinoma and inferior vena cava tumor. Considering that the hyperemia and edema[36,37] of tumor-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 peritumoral edema will be reduced, and the tumor will not continue to grow due to too long delay.

The clinical significances of this trial are as follows: ①For 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. ②For Mayo II-IV classification, preoperative radiotherapy + surgery may be better than surgery alone, which prolongs survival and reduces recurrence rate. ③When the tumor 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 tumors after radiotherapy have been proved to have prognostic significance in other tumors[22,39]. Tumors such as rectal cancer have clear grading standards, which are divided into 4 grades according to the degree of residual tumor after radiotherapy. Different grades correspond to

different prognoses. So far, this study is the only preoperative radiotherapy study in the world that focuses on tumor thrombus, and is also a pioneering study on the prognostic value of pathological changes after radiotherapy. Therefore, this study attempts to initially explore the post-radiotherapy changes of renal tumor thrombus, and judge the prognosis of the tumor 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. V2.30.

Recruitment began on 2018-05-01 and will be completed in 2021-12.

**Abbreviations**

AEs: adverse events; CRF: case report form; CTCAE: Common Terminology Criteria Adverse Events; ECOG: Eastern Cooperative Oncology Group; GTV: gross tumor volume; IVCTT: inferior vena cava tumor thrombus; OAR: organs at risk; PTV: planning target volume; RCC: Renal cell carcinoma; RFS: Recurrent-free survival; SABR: stereotactic ablative body radiotherapy; SBRT: stereotactic body radiotherapy

# Declarations

**Patient and Public Involvement**

Patients or the public will not be involved in the design, or conduct, or reporting, or dissemination plans of our research.

**Consent for publication**

Not applicable.

## Availability of data and materials

Researchers, monitors and reviewers of ethics committees will have access to the final trial dataset.

## Dissemination policy

Investigators and sponsor will communicate trial results to participants, healthcare professionals, the public, and other relevant groups via publication. The public will access to the full protocol, participant-level dataset, and statistical code from online database. Professional medical writers will complete an article of this trial.

## Authors' contributions

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

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## Competing interests statement

The authors declare that they have no competing interests.

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Figure 1. Flowchart for minimum assessments during treatment and follow up phase

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

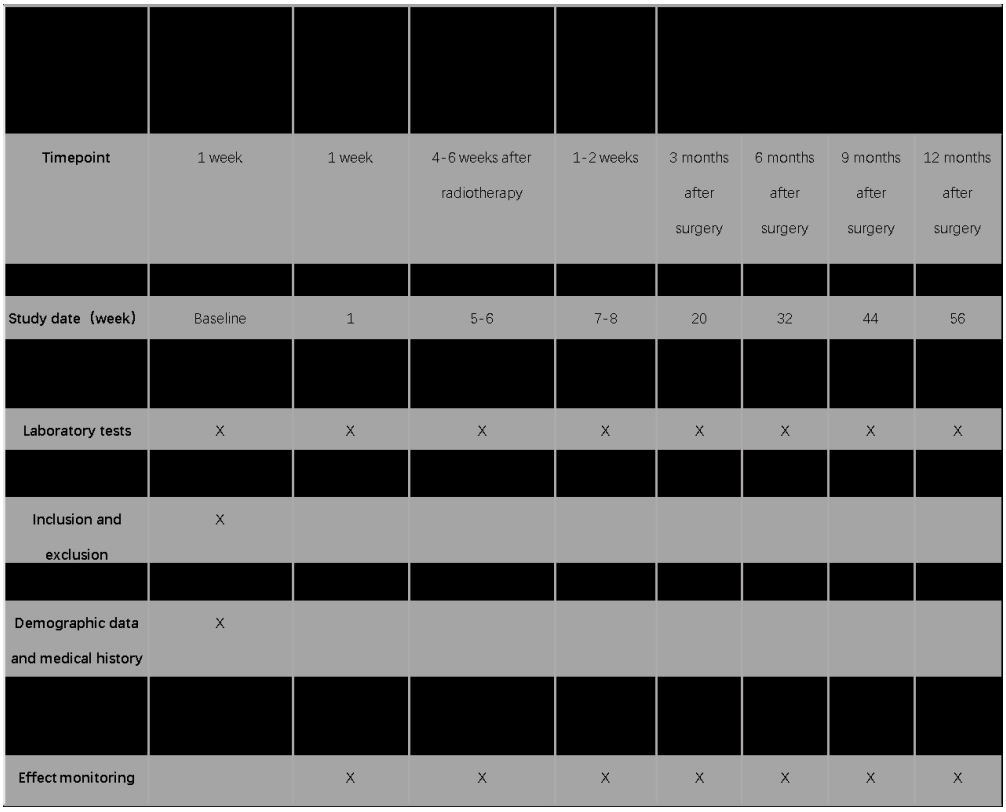


Figure 1. Flowchart for minimum assessments during treatment and follow up phase

215x173mm (150 x 150 DPI)

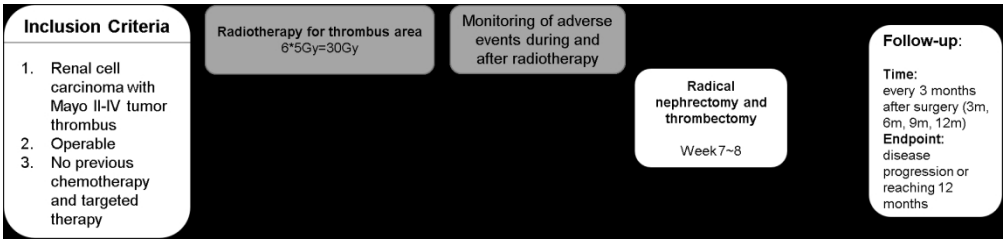


Figure 2. Schematic outline of the treatment plan. Patients with renal cell carcinoma with Mayo II-IV tumor thrombus will finish radiotherapy for thrombus area (total 30Gy). Radical nephrectomy and thrombectomy will be performed between week 7~8. Follow up for secondary endpoints will be starting at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

314x73mm (150 x 150 DPI)

Dear BMJ Open Editors:

On behalf of my co-authors, I am delighted to submit our protocol manuscript entitled " Preoperative stereotactic body radiotherapy combined with surgical treatment for renal cell carcinoma and inferior vena cava tumor thrombus: study protocol for a single-arm cohort trial" to your appreciation and the editorial analysis of the BMJ Open, as to the possibility of its publication.

In this manuscript, we developed a detailed study protocol aimed to evaluate the safety of preoperative stereotactic radiotherapy combined with surgical treatment of patients with renal cell carcinoma and inferior vena cava tumor thrombus (IVCTT). At present, the traditional treatment used for RCC combined with IVCTT is radical nephrectomy + IVC thrombectomy, which can improve patients' 5-year survival rate to 40%-60%. New methods are being urgently needed to further improve the survival rate of patients. We believe that this manuscript is of great value to all researchers interested in this particular complex disease.

Our Ethical Documentation was approved by the ethics committees of Peking University Third Hospital. The trial is funded by Peking University. Our study protocol has undergone peer-review by the funding body. Translated copies of the Ethical Documentation and the Funding Approval Documentation have been uploaded.

Our study status is ongoing and has not completed participant recruitment at the time of submission.

The manuscript has not been published before and is not being considered for publication elsewhere. No publications containing the results of this study have already been published or submitted to any journal. All authors have contributed to the creation of this manuscript for important intellectual content and read and approved the final manuscript, we declare there is no conflict of interest.

The number of words in this manuscript is 5724, which exceeds your limit, because according to SPIRIT's regulations, data entry, protocol amendments, quality control, stopping guidelines and other contents need to be added to this manuscript, which will take up more words.

Your kind consideration will be greatly appreciated.

With best regards,

Yours sincerely,

Lulin Ma
Peking University Third Hospital
E-mail: malulinpku@163.com

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description |
|---|---|---|
| **Administrative information** | | |
| Title | 1 | Title. |
| Trial registration | 2a | Line 29-32 |
| | 2b | N/A. This trial was registered on Chinese Clinical Trial Registry. |
| Protocol version | 3 | Line 338 |
| Funding | 4 | Line 363-366 |
| Roles and responsibilities | 5a | Line 1-5 & 359-362 |
| | 5b | Line 6 |
| | 5c | Line 359-362 |
| | 5d | Line 245-264 |
| **Introduction** | | |
| Background and rationale | 6a | Line 42-75 |
| | 6b | N/A. This is not a controlled trial and comparator is not applicable. |
| Objectives | 7 | Line 76-89 |
| Trial design | 8 | Line 92 |
| **Methods: Participants, interventions, and outcomes** | | |
| Study setting | 9 | Line 212-215 |
| Eligibility criteria | 10 | Line 93-110 |
| Interventions | 11a | Line 140-170 |
| | 11b | N/A. Not covered in our trial. |
| | 11c | N/A. Not covered in our trial. |

| | | |
|---|---|---|
| | 11d | N/A. Not covered in our trial. |
| Outcomes | 12 | Line 112-133 |
| Participant timeline | 13 | Figure 1&2. |
| Sample size | 14 | Line 134-139 |
| Recruitment | 15 | Line 141-143 |
| **Methods: Assignment of interventions (for controlled trials)** | | |
| Allocation: | | |
| Sequence generation | 16a | N/A. This is not a controlled trial. |
| Allocation concealment mechanism | 16b | N/A. This is not a controlled trial. |
| Implementation | 16c | N/A. This is not a controlled trial. |
| Blinding (masking) | 17a | N/A. This is not a controlled trial. |
| | 17b | N/A. This is not a controlled trial. |
| **Methods: Data collection, management, and analysis** | | |
| Data collection methods | 18a | Line 216-231 |
| | 18b | Line 232-233 |
| Data management | 19 | Line 234-240 |
| Statistical methods | 20a | Line 185-191 |
| | 20b | N/A. There are no additional analyses due to small sample size. |
| | 20c | Line 192-193 |
| **Methods: Monitoring** | | |
| Data monitoring | 21a | Line 245-264 |
| | 21b | Line 265-273 |
| Harms | 22 | Line 171-183 |
| Auditing | 23 | Line 246-249 |
| **Ethics and dissemination** | | |

| | | |
|---|---|---|
| Research ethics approval | 24 | Line 195-204 |
| Protocol amendments | 25 | Line 241-244 |
| Consent or assent | 26a | Line 196-199 |
| | 26b | N/A. Participant data and biological specimens will not be used in ancillary studies. |
| Confidentiality | 27 | Line 205-211 |
| Declaration of interests | 28 | Line 368 |
| Access to data | 29 | Line 353 |
| Ancillary and post-trial care | 30 | N/A. There is no compensation to those who suffer harm from trial participation except medical care. |
| Dissemination policy | 31a | Line 355-358 |
| | 31b | Line 355-358 |
| | 31c | Line 355-358 |
| **Appendices** | | |
| Informed consent materials | 32 | Line 196-199 |
| Biological specimens | 33 | N/A. No biological specimens will be used for genetic or molecular analysis. |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

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

| | |
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| Primary Subject Heading: | Urology |
| Secondary Subject Heading: | Radiology and imaging |
| Keywords: | RADIOTHERAPY, Urological tumours < UROLOGY, Kidney tumours < ONCOLOGY |
| | |

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

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## Abstract

**Introduction:** Although surgery is currently the first choice for patients with renal cell carcinoma and vena cava tumor 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 tumor thrombus. (3) The length of the tumor thrombus from the corresponding anatomical mark. (4) Invasion

of the inferior vena cava wall. (5) Recurrent-free survival (RFS) rate of the tumor. (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 tumor. (2) Lymph node condition.

**Main inclusion criteria:** Patients with renal cell carcinoma and inferior vena cava tumor 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:** ChiCTR1800015118. Clinical trials on the safety and effectiveness of neoadjuvant stereotactic radiotherapy combined with surgical treatment for patients with renal cell carcinoma with inferior vena cava tumor thrombus. Registered 08 March 2018, http://www.chictr.org.cn/showproj.aspx?proj=25747

**Keywords:** stereotactic ablative radiotherapy, renal cell carcinoma, inferior vena cava tumor thrombus, preoperative, safety

**Strengths and limitations of this study**

Strengths

- The only preoperative radiotherapy study in Asia that focuses on tumor thrombus
- A pioneering study on the prognostic value of pathological changes after radiotherapy

Limitations

- A single-arm study and no control group
- Small sample size

# Introduction

Renal cell carcinoma (RCC) is a common malignant tumor of the urinary system and accounts for 2~3% of adult malignant tumors[1]. Nearly 1/3 of the patients on presentation are locally advanced tumors (2010 AJCC renal cancer stage III or IV) at the time of diagnosis[2]. RCC has a tendency for venous invasion and 4% to 10% of newly diagnosed cases have inferior vena cava tumor 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 summarized 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. ③ When the tumor thrombus invades the inferior vena cava wall in a wide range, segmental resection of the inferior vena cava is required[10]. Lower limb edema 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 tumors and surrounding normal tissues to obtain completely different doses. Image-guided technology allows the doses given from the radiotherapy plan to hit the tumor 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 renal cell carcinoma 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 tumor thrombus, increase surgical resection rate, and reduce surgical risk. Evidence has shown that SABR can reduce the transverse diameter of the tumor thrombus[18], which may help solve the problem of venous obstruction by tumor thrombus. And the team's long-term follow-up results of two cases showed that SABR to RCC with IVCTT could get good local tumor 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 renal cell carcinoma and inferior vena cava tumor thrombus. 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) v4.0. 2. Secondary purpose: To identify whether the difficulty or risk of surgery is increased after radiotherapy by analyzing 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. 3. When the tumor 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 ≥ 18 years old.

(2) Imaging examination of renal cell carcinoma with inferior vena cava tumor thrombus.

(3) Inferior vena cava tumor thrombus graded from Mayo II to Mayo IV.

(4) Subjects eligible for SABR for IVC tumor 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 renal cell carcinoma or inferior vena cava tumor thrombus.

(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 judgment 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 tumor thrombus. Measurement time point: before and after radiotherapy. Measurement method: CT or MRI.

(3) The length of the tumor 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 (RFS) rate of the tumor. 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 tumor. 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 "Neo-adjuvant SABR for IVC Tumor Thrombus in Newly Diagnosed RCC"[20] retrieved on the Clinical trial website. It's 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**

20 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 utilized 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 tumor ≥15cm upward, and the lower boundary ≥15cm as the scanning range. CT images include unenhanced phase (as the reference image), arterial phase, and venous phase with a slice thickness of 1-1.5mm. MRI images include T1WI, T2WI, enhanced and DWI phases with a slice thickness of 1-3mm. 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 tumor thrombus as gross tumor volume (GTV) and stomach, duodenum, jejunum, ileum, colon, spinal cord, liver, esophagus as organs at risk (OAR). The planning target volume (PTV) is generated by adding a 3mm margin around the GTV. On day 3, a prescription dose of PTV 30Gy/5Gy/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 Inc., Sunnyvale, CA) treatment planning system. On day 4, cyberknife (CyberKnife ® VSI™, Accuray Inc., Sunnyvale, CA) 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, re-admission to finish blood routine, blood biochemistry, coagulation function, urine routine, enhanced CT of the urinary system, enhanced MRI of inferior vena cava on re-admission day 1. Complete pre-operation preparations on re-admission day 3. Radical nephrectomy + IVC thrombectomy will be performed on re-admission day 4.

Post-surgery 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 figure of detailed flowchart 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 Common Terminology Criteria for Adverse Events (CTCAE) v4.0. We are interested in acute and late toxicity including nausea, fatigue, anorexia, diarrhea, enteritis, gastritis, fistula, dermatitis, anemia, lymphopenia, neutropenia, thrombocytopenia, and ALT/AST elevation. Severe toxicity is defined as grade III-IV toxicity according to CTCAE v4.0.

Modified Clavien classification system[21] is used to evaluate adverse events in terms of surgery. Surgical AEs of interest are postoperative active bleeding, postoperative anemia, wound infection, pulmonary infection, lower extremity deep vein thrombosis, pulmonary embolism, chylous fistula, renal dysfunction, hyperkalemia, and continuous venovenous hemodiafiltration.

If any serious adverse event or important adverse event 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 chi square test is used. Rank sum test is used to compare the rank data. The measurement data are expressed by means + standard deviation. 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 tumor-free rate, tumor-specific survival rate, and overall survival rate with SPSS 18.0 software, and the Log-rank test will be performed. The comparability of data and the comparison of short-term efficacy before and after the test will be tested by Fisher's exact probability method. $P<0.05$ 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 the supplementary 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 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, ID 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 organization**

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 case report form 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 case report forms 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, adverse event 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 case report form will be archived and stored in the order of numbers, and filled with a search catalog 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 center shall objectively and truthfully record and retain all data and the execution and modification of the program 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 judgment standards.

(5) The investigator will fill in the case report form according to the requirements, truthfully, in detail, and carefully record the contents of the CRF to ensure that the content of the case report form 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 program 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 renal cell carcinoma and inferior vena cava tumor thrombus.

Preoperative radiotherapy has been proven effective in many tumors, including rectal cancer,

esophageal cancer, and soft tissue sarcoma. Taking rectal cancer as an example, compared with surgery alone, the effects of preoperative radiotherapy are mainly reflected in ①Reducing clinical staging and increasing surgical resection rate[22]. ② Increasing anus preservation rate and improving patients' quality of life[23]. ③Reducing 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 randomized 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 tumors 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 (SBRT), uses high-precision radiotherapy technology to focus the radical radiation dose (single dose> 8-10 Gy) to the tumor site through external irradiation to achieve the purpose of radical treatment of the tumor. 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 tumors such as liver cancer, lung cancer, and spinal tumors in recent years, with definite curative effect[30]. SABR was firstly clinically applied for stage I non-small cell lung carcinoma, and related literature reports that the long-term local tumor control rate can reach 90%[31].

In the existing researches on the treatment of renal cell carcinoma with SABR, the separated fractions and radiation doses are different. A study[16] found that the SABR regimen with 4 fractions and a total radiation dose of 48 Gy has no significant dose-related adverse reactions, which is safe and feasible for patients with localized renal cell carcinoma. Another study[13] recommended using 5 fractions and a total radiation dose of 35Gy to treat patients with inoperable metastatic renal cancer. The existing lead-in

trial results of SABR for RCC with IVCTT with a dose of 40Gy in 5 fractions has shown safety[32]. Most SABR protocols often use 3 to 5 fractions[33,34]. We choose tumor thrombus as the target organ of radiotherapy, not including renal cancer tissue, to avoid the difficulty of surgical separation of the kidney due to edema, fibrosis, or other reasons after irradiation. Since the growth level of the tumor thrombus usually coincides with the horizontal part of the duodenum, the duodenal perforation will happen if the radical dose of the tumor 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 - 30Gy with 5 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 renal cell carcinoma and inferior vena cava tumor. Considering that the hyperemia and edema[36,37] of tumor-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 peritumoral edema will be reduced, and the tumor will not continue to grow due to too long delay.

The clinical significances of this trial are as follows: ①For 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. ②For Mayo II-IV classification, preoperative radiotherapy + surgery may be better than surgery alone, which prolongs survival and reduces recurrence rate. ③When the tumor 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 tumors after radiotherapy have been proved to have prognostic significance in other tumors[22,39]. Tumors such as rectal cancer have clear grading standards, which are divided into 4 grades according to the degree of residual tumor after radiotherapy. Different grades correspond to

different prognoses. So far, this study is the only preoperative radiotherapy study in the world that focuses on tumor thrombus, and is also a pioneering study on the prognostic value of pathological changes after radiotherapy. Therefore, this study attempts to initially explore the post-radiotherapy changes of renal tumor thrombus, and judge the prognosis of the tumor 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. V2.30.

Recruitment began on 2018-05-01 and will be completed in 2021-12.

**Abbreviations**

AEs: adverse events; CRF: case report form; CTCAE: Common Terminology Criteria Adverse Events; ECOG: Eastern Cooperative Oncology Group; GTV: gross tumor volume; IVCTT: inferior vena cava tumor thrombus; OAR: organs at risk; PTV: planning target volume; RCC: Renal cell carcinoma; RFS: Recurrent-free survival; SABR: stereotactic ablative body radiotherapy; SBRT: stereotactic body radiotherapy

# Declarations

**Patient and Public Involvement**

Patients or the public will not be involved in the design, or conduct, or reporting, or dissemination plans of our research.

**Consent for publication**

Not applicable.

## Availability of data and materials

Researchers, monitors and reviewers of ethics committees will have access to the final trial dataset.

## Dissemination policy

Investigators and sponsor will communicate trial results to participants, healthcare professionals, the public, and other relevant groups via publication. The public will access to the full protocol, participant-level dataset, and statistical code from online database. Professional medical writers will complete an article of this trial.

## Authors' contributions

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

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## Competing interests statement

The authors declare that they have no competing interests.

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Figure 1. Flowchart for minimum assessments during treatment and follow up phase

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

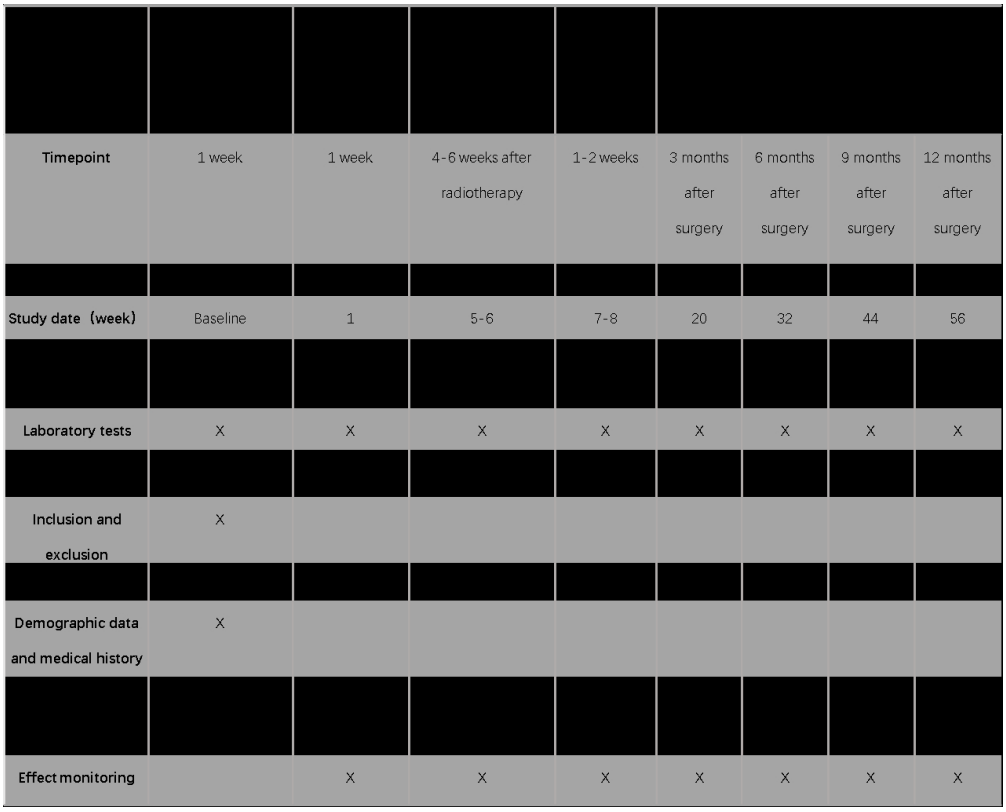


Figure 1. Flowchart for minimum assessments during treatment and follow up phase

215x173mm (150 x 150 DPI)

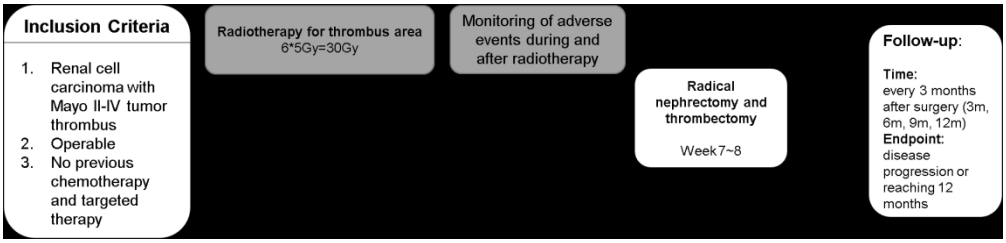


Figure 2. Schematic outline of the treatment plan. Patients with renal cell carcinoma with Mayo II-IV tumor thrombus will finish radiotherapy for thrombus area (total 30Gy). Radical nephrectomy and thrombectomy will be performed between week 7~8. Follow up for secondary endpoints will be starting at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

314x73mm (150 x 150 DPI)

# Informed Consent Form

## Clinical trials on the safety and effectiveness of neoadjuvant stereotactic radiotherapy combined with surgical treatment for patients with renal cell carcinoma with inferior vena cava tumor thrombus

**You are invited to participate in this study because you meet the following Inclusion criteria:**

(1) Age ≥ 18 years old.

(2) Imaging examination of renal cell carcinoma with inferior vena cava tumor thrombus.

(3) Inferior vena cava tumor thrombus graded from Mayo II to Mayo IV.

(4) Oncologists believe that patients are suitable for preoperative stereotactic ablative body radiotherapy (SABR) to treat inferior vena cava tumor thrombus.

(5) Urologists believe that patients are suitable for radical nephrectomy and inferior vena cava thrombectomy to treat renal cancer and inferior vena cava tumor thrombus.

(6) ECOG 0-2.

(7) Able to complete enhanced CT or enhanced MRI (either one) examination.

(8) Able to sign this Informed Consent Form.

Your research doctor or research staff will fully explain the contents of the informed consent form for you. Please carefully read this informed consent form and make a cautious decision whether to participate in the study. If you are participating in another research, please inform your research doctor or research staff.

The content / nature, risks and other important information of this study are as follows:

Director Ma Lulin will carry out this study.

### I. Why to conduct this research?

(I) The background of this study is as follows:

Stereotactic radiotherapy (SBRT) or stereotactic ablation radiotherapy (SABR) refers to precise and concentrated radiotherapy for lesions outside the brain, which is given in small fractions (single dose belongs to the ablation dose range). With the progress of technology and the accumulation of experience, stereotactic radiotherapy technology has become more and more sophisticated and rapid. In recent years, a systematic review of 10 studies involving 126 patients with primary renal cell carcinoma who lost the chance of surgery shows that the weighted local control rate is 92.9% and the weighted severe toxicity is 3.8%. Recent prospective studies continue to show that short-term and medium-term local control rates are generally higher than 90% with low toxicity, similar to the previous studies. The main acute toxicity reported in the literature is self-limited nausea and fatigue, followed by radiation dermatitis and enteritis. Reported severe toxicities include nephrotoxicity, duodenal ulcer and skin toxicity, but the overall incidence of all these toxicities is very low (< 5% of patients).

Radical nephrectomy + inferior vena cava thrombectomy is a traditional and effective

treatment for renal cell carcinoma with inferior vena cava tumor thrombus.

The research unit has all the diagnostic and therapeutic conditions involved in the protocol. The level of urology surgery in our hospital is in the lead in China. There are a group of clinical experts specialized in renal cell carcinoma with inferior vena cava tumor thrombus, who can ensure that the enrolled patients receive standard preoperative radiotherapy and surgical treatment.

(II) The purpose of this study is as follows:

To determine the safety of the treatment by the study of preoperative stereotactic radiotherapy combined with surgical treatment of patients with renal cell carcinoma and inferior vena cava tumor thrombus. 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) v4.0. 2.To identify whether the difficulty or risk of surgery is increased after radiotherapy by analyzing perioperative complications, operation time, intraoperative bleeding volume, intraoperative transfusion volume of suspended red blood cells, and postoperative hospital stay. Secondary purpose: 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. 3. When the tumor 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 tumors after radiotherapy have been proved to have prognostic significance in other tumors. Tumors such as rectal cancer have clear grading standards, which are divided into 4 grades according to the degree of residual tumor after radiotherapy. This study attempts to initially explore the post-radiotherapy changes of renal tumor thrombus, and judge the prognosis of the tumor according to the different pathological changes.

**II. How many people will participate in this research?**

Approximately 20 people will participate in this research conducted by our center at Peking University Third Hospital, and approximately 15 people will participate in this research at Peking University Third Hospital.

**III. What are the contents of this research?**

(I) Study design

This study is a non-randomized controlled study, which is not suitable for blind method. According to the registered clinical trial study "Neo advanced SABR for IVC tumor thrombus in newly diagnosed RCC" retrieved from the clinical trail website, the study sample size was divided into two groups, 15 cases in each group. However, there is only one intervention group in our study. After the intervention, a self-control study will be conducted. The purpose is to focus on the safety and effectiveness of the trial. The sample size is estimated to be 20 cases.

(II) Inclusion and exclusion criteria

Inclusion criteria:

1) Age ≥ 18 years old.

2) Imaging examination of renal cell carcinoma with inferior vena cava tumor thrombus.

3) Inferior vena cava tumor thrombus graded from Mayo II to Mayo IV.

4) Oncologists believe that patients are suitable for preoperative stereotactic ablative body radiotherapy (SABR) to treat inferior vena cava tumor thrombus.

5) Urologists believe that patients are suitable for radical nephrectomy and inferior vena cava thrombectomy to treat renal cancer and inferior vena cava tumor thrombus.

6) ECOG 0-2.

7) Able to complete enhanced CT or enhanced MRI (either one) examination.

8) Able to sign this Informed Consent Form.

Exclusion criteria:

1) Subjects with a history of radiotherapy in the area of renal cell carcinoma or inferior vena cava tumor thrombus.

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 judgment of patients, such as mental disorders.

(III) Research process

1. Before you are enrolled in the study, the doctor will ask and record your medical history, and perform blood routine test, blood biochemistry test, blood coagulation function test, urine routine test, urinary system enhanced CT, abdominal enhanced MRI, and renal dynamic imaging.

If you are a qualified participant, you can participate in the study voluntarily and sign the informed consent form.

If you are not willing to participate in the study, we will treat you according to your wishes.

2. If you agree to participate in this study and sign the informed consent form, you will accept the examination and process related to the trial according to the protocol to confirm whether you are suitable to participate in this study:

The research content process of this project:

(1) On the 1st day after admission, you will have a pre-radiotherapy location check to complete the pre-radiation preparations;

(2) On the 2-7 days after admission, you will have preoperative radiotherapy;

(3) After 4-6 weeks of rest, on the 1st day of re-admission you will have blood routine test, blood biochemistry test, urine routine test, coagulation function test, enhanced CT of the urinary system, and enhanced MRI of the inferior vena cava;

After the research content of this project, the routine diagnosis and treatment project process:

(4) On the 3rd day of re-admission, complete the pre-operation preparations;
(5) On the 4th day of re-admission, you will receive routine surgical treatment;
(6) On the 1st day after surgery, you will have blood routine, blood biochemistry, urine routine, erythrocyte sedimentation rate, and coagulation function tests to complete the assessment of your recovery after the operation. At the same time, you will receive conventional intravenous medication after surgery.
(7) On the 2nd day after surgery, you will have blood routine, blood biochemistry, urine routine, erythrocyte sedimentation rate, and coagulation function tests to complete the assessment of your recovery after the operation. At the same time, you will receive conventional intravenous medication after surgery.
(8) On the 3rd day after the operation, you will have blood routine, blood biochemistry, urine routine, erythrocyte sedimentation rate, and coagulation function tests to complete the assessment of your recovery after the operation. At the same time, you will receive conventional intravenous medication after surgery.
(9) On the 7th day after surgery, you will have blood routine, blood biochemistry, urine routine, erythrocyte sedimentation rate, and coagulation function tests to complete the assessment of your recovery after the operation.
(10) On the day of discharge after surgery, you will have blood routine, blood biochemistry, urine routine, erythrocyte sedimentation rate, and coagulation function tests to complete the assessment of your recovery after the operation.
(11) Every day after the operation, a urology doctor with a title of deputy chief or above will conduct ward rounds to closely observe your condition. Your postoperative pathology will be evaluated by a professional pathologist;
(12) 3 months, 6 months, 9 months, and 12 months after surgery, please go to the outpatient clinic for follow-up in time, and we will also conduct a telephone follow-up.

3. For the study of discarded tissues after routine clinical surgery / operation: our research materials are from discarded tissues after routine clinical surgery / operation, and the enrollment test will not expand the scope of your surgery / operation, nor will it increase the number of specimens.

4. Drugs or procedures prohibited in the study:
None.

5. What do I need to do to participate in the research?
You must come to the hospital with a copy of the medical record and the medical follow-up form according to the follow-up time agreed by the doctor and yourself (during the follow-up period, the doctor may know your situation by telephone or on-site). Your follow-up is very important because the doctor will judge whether the treatment you received really works and guide you in time.
According to your condition, if you need to take medicines related to renal cancer treatment after surgery, you must follow the instructions of your doctor, and please fill in your medication records in a timely and objective manner. At each follow-up, you must return the unused medicines and their packages, and bring other medicines you are taking, including those that you must continue to take if you have other comorbid diseases.

You cannot use other medicines for kidney cancer during the study period. If you need other treatments, please contact your doctor in advance.

(IV) How long will this research last?

3 months, 6 months, 9 months, and 12 months after surgery, please go to the outpatient clinic for follow-up in time. We will also conduct a 2-year telephone follow-up based on your condition.

You can decide to withdraw from the study at any time without losing any benefits you should have received. However, if you decide to withdraw during the course, taking into account your safety issues, it is possible that a related medical examination will be carried out after withdrawal.

(V) What are the risks of participating in this study?

In addition to the risks in the conventional treatment process (before taking a certain treatment measure, we will explain the risks of the treatment in detail and sign an additional informed consent form with you), participating in this study may have the following risks. At the same time, we have prepared the relevant treatment plan and possible compensation plan:

(1) Radiotherapy injury: the possibility of duodenum, liver, and spinal cord injury.

(2) Radiotherapy toxicity: the possibility of skin toxicity, nausea, loss of appetite, vomiting and diarrhea, weight loss, frequent urination, urgency, pancytopenia, liver failure, and renal failure.

(3) During radiotherapy, the tumor thrombus may become loose, and the proximal end may fall off to the heart, which may cause pulmonary embolism and threaten life, and pulmonary embolectomy may be required.

(4) There may be undiscovered or unpredictable adverse events.

Solution:

(1) If duodenal injury occurs, it may need fasting, rehydration, gastrointestinal decompression, acid suppression, pain relief, parenteral nutrition and other treatment, or even surgery.

(2) If liver damage occurs, hepatoprotective treatment may be required.

(3) If spinal cord injury occurs, it may require diuresis, detumescence, cortisol hormone therapy, and surgery if necessary.

(4) If radiotherapy-related toxicity occurs, we treat it symptomatically.

If you experience any discomfort or new changes in your condition during the study period, or any unexpected situation, regardless of whether it is related to the study, you should notify your doctor in time, and he/she will make judgment and give appropriate medical treatment.

During the study period, you need to go to the hospital on time for follow-up and examinations, which may take up some of your time and may cause trouble or inconvenience to you.

For female subjects:

During the study period, pregnancy brings great risks to unborn children, some of which are unpredictable at present. Therefore, pregnant women will not be recruited as subjects in this study. If you are in childbearing age (including one year after amenorrhea), you will be tested for pregnancy (venous blood should be taken for examination), and the test result must be negative before you can continue to participate in this study. If you have sex, you must agree to take appropriate contraceptive measures during the course of the study and in the following months. If you are pregnant or have unprotected sex during the study, please inform your research doctor immediately.

For male subjects:
Participation in this study may damage your sperm and the children you gave birth to during the study. The damage is currently unpredictable. If you have sex, you must agree to use medically approved contraception during the course of the study and in the following months. Please inform your partner of this risk to the unborn baby. She should understand that if she is pregnant, you need to inform your research doctor immediately, and she should also inform her doctor immediately.

(VI) Drug interactions:
For safety reasons, you must inform the research doctor or nurse of all prescription drugs, traditional Chinese medicine products, over-the-counter drugs, vitamins, natural supplements and other health products you are taking before the start of the study. Be sure to tell your research doctor or nurse before taking these drugs during the study.

**IV. What are the benefits of participating in the research?**

If you agree to participate in this study, you may have direct medical benefits. For example: 1. Reduce the difficulty of operation, blood loss, blood transfusion rate and perioperative complications; 2. In this study, preoperative stereotactic radiotherapy (SBRT) as an adjuvant surgery may be better than surgery alone, which may prolong the survival time and reduce the recurrence rate; 3. When the tumor thrombus invades the wall of inferior vena cava in a wide range, preoperative radiotherapy can be used to preserve the wall of inferior vena cava.

We hope that the information obtained from your participation in this study will benefit patients with the same condition as yours in the future.

Although there is already evidence that radiotherapy has a satisfactory effect on patients with renal cell carcinoma and tumor thrombus, it can not guarantee that it will be effective for you, and you may not have the above benefits. The preoperative stereotactic radiotherapy (SBRT) is not the only way to treat renal cell carcinoma with venous tumor thrombus. If preoperative stereotactic radiotherapy (SBRT) is not effective for your condition, you can ask your doctor about possible alternative treatment.

**V. Alternative medical options?**

If you do not participate in this study, you have the following options:

- Surgery alone
- Radiotherapy alone
- Surgery combined with postoperative adjuvant therapy (radiotherapy, chemotherapy, targeted therapy, etc.)
- Palliative treatment

**VI. Will my information be kept confidential?**

We will keep your research records confidential as required by law. The relevant laws of our country provide guarantees for the security of privacy, data and authorized access. Regarding your research information, we will use a unique number to represent you, and the coded information will be properly stored in Peking University Third Hospital. Your identity will not be disclosed when the research information and data obtained from this study are published in scientific conferences or scientific journals. However, in order to ensure that the study meets the requirements of relevant laws and regulations, your records may be reviewed. The reviewers include the relevant national administrative departments and the Ethics Committee of Peking University Third Hospital. We will make every effort to protect the privacy of your personal medical data within the scope permitted by law.

**VII. About research expenses?**

The patients are responsible for all the costs of the project. If participation in this study brings potential additional costs to the subjects, the patients will also be responsible for all the costs, and the patients will not be compensated for these costs. The treatment and examination required for comorbidities will not be free.

**VIII. What compensation can I get?**

You will not be compensated for your participation in this study.

**IX. In case of study related injury**

Doctors will do their best to prevent and treat the possible injuries caused by this study. If you are injured due to participating in the study, the Department of Urology and Oncology Radiotherapy of Peking University Third Hospital will immediately provide necessary medical care, and bear the cost of treatment and corresponding financial compensation in accordance with related laws and regulations. Please contact director Ma Lulin on 15611908062.

If there are adverse events in clinical trials, the medical expert committee will identify whether they are related to this study. The sponsor will provide the cost of treatment and corresponding financial compensation for the damage related to the trial in accordance with the provisions of China's "drug clinical trial quality management standard".

**X. Refusal or withdrawal from the study**

Your participation in the trial is voluntary. You can refuse to participate or withdraw from the trial in any way at any stage of the trial without discrimination or retaliation. Your medical treatment and rights will not be affected, but all unused research drugs and devices should be returned. After you quit, we will not collect any new data related to you in the future, and will destroy the research data previously collected and the data withdrawn due to adverse reactions.

If you have serious adverse reactions or your research doctor feels that it is not in your best interest to continue to participate in the study, he will decide to withdraw you from the study. If this happens, we will inform you in time and your research doctor will discuss with you other options you have. If the doctor thinks that the sudden interruption of the trial will affect your health, he may ask you to have a check-up in the hospital before stopping the trial.

**XI. Related consultation**

If you have any questions related to this study, please contact director Ma Lulin at 15611908062.

If you have any questions related to your own rights and interests, or you want to reflect your dissatisfaction and worries in the process of participating in this study, please contact the Comprehensive Research Ethics Office of Peking University Third Hospital at 010-82265571.

**XII. What should I do now?**

It's up to you (and your family) to decide whether to participate in the study.

Before you make a decision to participate in the study, please ask your doctor about the relevant questions as many as possible.

Thank you for reading the above materials. If you decide to participate in this study, please tell your doctor and he will arrange all matters related to the study for you. Please keep this information.

**XIII. Informing statement**

"I have informed the subject of the research background, purpose, procedures, risks and benefits of the clinical study on the safety and effectiveness of neoadjuvant stereotactic radiotherapy combined with surgical treatment for patients with renal cell carcinoma with inferior vena cava tumor thrombus. I have given him / her enough time to read the informed consent, discuss with others, and answer his / her research questions; I have told the subject to contact director Ma Lulin whenever he encounters problems related to the research, and to contact the Comprehensive Research Ethics Office of Peking University Third Hospital whenever he encounters problems related to his own rights / interests, and provide accurate contact information; I have informed the subject that he can

withdraw from the study at any time without any reason; I have informed the subject that he / she will receive a copy of this informed consent form, which contains my signature and his / her signature."

Signature of the researcher who obtained the informed consent_____
Contact telephone number_____
Date_____

**XIV. Informed consent statement**

"I have been informed of the background, purpose, procedures, risks and benefits of the clinical study on the safety and effectiveness of neoadjuvant stereotactic radiotherapy combined with surgical treatment for patients with renal cell carcinoma with inferior vena cava tumor thrombus. I have enough time and opportunity to ask questions, and I am very satisfied with the answers. I have also been told who I should contact when I have questions, dissatisfaction, concerns or want further information. I have read this informed consent and agree to participate in this study. I promise that the information and test results provided to the researchers are true and valid. I know that I can withdraw from this study at any time without any reason. I have been told that I will be given a copy of this informed consent form, which contains the signatures of me and the researcher."

Signature of the subject_____
Contact telephone number_____
Date_____

**When the subject is unable to sign, the following method is allowed:**

The relationship between the legal representative and the subject: _____
Signature of the legal representative_____
Contact telephone number_____
Date_____

Press the fingerprint: