

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-055364
Article Type:	Protocol
Date Submitted by the Author:	10-Jul-2021
Complete List of Authors:	Liu, Yunchong; Peking University Third Hospital, Liu, Zhuo; Peking University Third Hospital, Department of Urology Peng, Ran; Peking University Third Hospital, Department of Radiation Oncology Xiao, Ruotao; Peking University Third Hospital, Department of Urology Wang, Junjie; Peking University Third Hospital, Department of Radiation Oncology Wang, Hao; Peking University Third Hospital, Department of Radiation Oncology Ma, Lulin; Peking University Third Hospital, Department of Urology
Keywords:	RADIOTHERAPY, Urological tumours < UROLOGY, Kidney tumours < ONCOLOGY

SCHOLARONE™
Manuscripts

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

1 Yunchong Liu^{1†}, Zhuo Liu^{1†}, Ran Peng^{2†}, Ruotao Xiao¹, Junjie Wang², Hao Wang² and
2 Lulin Ma^{1*}

3 ¹Department of Urology, Peking University Third Hospital, Beijing 100191, China.

4 ²Department of Radiation Oncology, Peking University Third Hospital, Beijing 100191, China.

5 [†]Yunchong Liu, Zhuo Liu, and Ran Peng contributed equally to this work.

6 ^{*}Correspondence: malulinpku@163.com.

7 Abstract

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

13 **Methods and analysis:**

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

15 **Study treatment:** Preoperative stereotactic ablative radiotherapy combined with surgical treatment.

16 **Primary endpoint:** (1) Adverse reactions after 4-6 weeks of SABR. (2) Perioperative indicators
17 including operation time, intraoperative bleeding volume, and postoperative complications.

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

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

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

26 **Planned sample size:** 20 patients.

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

29 **Trial registration:** ChiCTR1800015118. Clinical trials on the safety and effectiveness of neoadjuvant
30 stereotactic radiotherapy combined with surgical treatment for patients with renal cell carcinoma with
31 inferior vena cava tumor thrombus. Registered 08 March 2018,
32 <http://www.chictr.org.cn/showproj.aspx?proj=25747>

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

35 **Strengths and limitations of this study**

36 Strengths

- 37 ● The only preoperative radiotherapy study in the world that focuses on tumor thrombus
- 38 ● A pioneering study on the prognostic value of pathological changes after radiotherapy
- 39 limitations
- 40 ● A single-arm study and no control group
- 41 ● Small sample size

42 Introduction

43 Renal cell carcinoma (RCC) is a common malignant tumor of the urinary system and accounts for 2~3%
44 of adult malignant tumors^[1]. Nearly 1/3 of the patients on presentation are locally advanced tumors
45 (2010 AJCC renal cancer stage III or IV) at the time of diagnosis^[2]. RCC has a tendency for venous
46 invasion and 4% to 10% of newly diagnosed cases have inferior vena cava tumor thrombus (IVCTT)^[3].
47 Currently, the traditional treatment used for RCC combined with IVCTT is surgery. Commonly used
48 surgical methods are open or laparoscopic radical nephrectomy + IVC thrombectomy^[4,5], which have a
49 high risk and require extremely proficient operating skills and surgical capabilities of the doctor. Open
50 or laparoscopic surgery may have early postoperative complications, such as bleeding, lung infection,
51 deep vein thrombosis of the lower limbs, pulmonary embolism, renal failure, liver failure, urinary fistula,
52 chylous fistula, and so on. Severe complications can even lead to death^[3].

53 At present, the main problems in the treatment of RCC combined with IVCTT can be summarized in
54 the following aspects: ① The operation is with high difficulties, risks, and many complications^[3]. ②
55 For Mayo I -IV grade, radical nephrectomy + IVC thrombectomy can improve the 5-year survival rate
56 of patients, but it can only reach 40%-60%^[6]. How to further improve the survival rate of patients is a
57 hot research topic. ③ When the tumor thrombus invades the inferior vena cava wall in a wide range,
58 segmental resection of the inferior vena cava is required^[7]. Lower limb edema and renal insufficiency
59 may occur after surgery.

60 Nowadays, the equipment, technology, and concept of radiotherapy have ushered in a leap-forward
61 development. The development of intensity-modulated radiotherapy technology has allowed tumors and
62 surrounding normal tissues to obtain completely different doses. Image-guided technology allows the
63 doses given from the radiotherapy plan to hit the tumor accurately. Stereotactic ablative body
64 radiotherapy (SABR) has greatly expanded and partially subverted the understanding of traditional
65 radiobiology. In the past 10 years, new explorations of renal cancer have been continuously reported,
66 mainly confined to inoperable renal cancer patients, all using SABR technology, and its local control

67 rate and survival rate have reached a high level^[8-13].
68 Combined with the good results achieved by the SABR technique in inoperable renal cancer patients,
69 we expect that it can shrink and reduce the level of tumor thrombus, increase surgical resection rate,
70 and reduce surgical risk. Up till now, there is only one case report^[14] about SABR for renal cell
71 carcinoma with tumor thrombus. Its safety and effectiveness need to be further examined.

72 **Aims**

73 To determine the safety of the treatment by the study of preoperative stereotactic radiotherapy combined
74 with surgical treatment of patients with renal cell carcinoma and inferior vena cava tumor thrombus.
75 Main purpose: 1. To identify the acute and late toxicity of radiotherapy. Severe toxicity is defined as
76 grade III-IV toxicity according to Common Terminology Criteria Adverse Events (CTCAE) v4.0. 2.To
77 identify whether the difficulty or risk of surgery is increased after radiotherapy by analyzing
78 perioperative complications, operation time, intraoperative bleeding volume, intraoperative transfusion
79 volume of suspended red blood cells, and postoperative hospital stay. Secondary purpose: Using the
80 follow-up data of the patients to clarify the curative effect of the treatment: 1. For Mayo III-IV
81 classification, it may reduce the difficulty of operation, blood loss, blood transfusion rate and
82 perioperative complications. 2. For Mayo II-IV classification, preoperative radiotherapy + surgery may
83 be better than surgery alone, which prolongs survival and reduces recurrence rate. 3. When the tumor
84 thrombus invades the inferior vena cava wall in a wide range, preoperative radiotherapy can be used to
85 preserve the inferior vena cava vessel wall.

86 **Methods and Analysis**

87 **Study design**

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

1
2
3 **89 Inclusion criteria**

4
5
6 90 (1) Age \geq 18 years old.

7
8 91 (2) Imaging examination of renal cell carcinoma with inferior vena cava tumor thrombus.

9
10 92 (3) Inferior vena cava tumor thrombus graded from Mayo II to Mayo IV.

11
12 93 (4) Oncologists believe that patients are suitable for preoperative stereotactic ablative body
13
14 94 radiotherapy (SABR) to treat inferior vena cava tumor thrombus.

15
16 95 (5) Urologists believe that patients are suitable for radical nephrectomy and inferior vena cava
17
18 96 thrombectomy to treat renal cancer and inferior vena cava tumor thrombus.

19
20 97 (6) ECOG 0-2.

21
22 98 (7) Able to complete enhanced CT or enhanced MRI (either one) examination.

23
24
25 **99 Exclusion criteria**

26
27
28
29 100 (1) Subjects with a history of radiotherapy in the area of renal cell carcinoma or inferior vena cava
30
31 101 tumor thrombus.

32
33 102 (2) Subjects with a history of preoperative targeted therapy, preoperative chemotherapy, or other
34
35 103 related treatments.

36
37 104 (3) Subjects with a history of pulmonary embolism.

38
39 105 (4) Subjects with severe cardiopulmonary insufficiency, severe arrhythmia, myocardial infarction,
40
41 106 angina pectoris, severe coagulation disease, or severe liver disease that cannot tolerate SABR or surgery.

42
43 107 (5) Subjects with diseases that severely affect the judgment of patients, such as mental disorders.

44
45
46 **108 Endpoints**

47
48
49 **109 Primary endpoints**

50
51
52 110 (1) Adverse reactions after 4-6 weeks of SABR. Measurement time point: 4-6 weeks after SABR
53
54 111 treatment. Measurement method: observation and inspection.

55
56 112 (2) Perioperative indicators including operation time, intraoperative bleeding volume, and

1
2
3 113 postoperative complications. Measurement time point: postoperative. Measurement method: surgical
4
5 114 record or observation and inspection.
6
7

8 115 *Secondary endpoints*
9

10
11 116 (1) Mayo staging of tumor thrombus. Measurement time point: before and after radiotherapy.
12
13 117 Measurement method: CT or MRI.

14
15 118 (2) The length of the tumor thrombus from the corresponding anatomical mark. Measurement time
16
17 119 point: before and after radiotherapy. Measurement method: CT or MRI.

18
19 120 (3) Invasion of the inferior vena cava wall. Measurement time point: before and after radiotherapy.
20
21 121 Measurement method: CT or MRI.

22
23 122 (4) The longest diameter of the tumor. Measurement time point: before and after radiotherapy.
24
25 123 Measurement method: CT or MRI.

26
27 124 (5) Lymph node condition. Measurement time point: before and after radiotherapy. Measurement
28
29 125 method: CT or MRI.

30
31 126 (6) Recurrent-free survival (RFS) rate of the tumor. Measurement time point: postoperative.
32
33 127 Measurement method: CT or MRI, follow-up.

34
35 128 (7) Cancer-specific survival rate. Measurement time point: postoperative. Measurement method:
36
37 129 follow-up.

38
39 130 (8) Overall survival rate. Measurement time point: postoperative. Measurement method: follow-up.
40

41
42 131 **Statistical calculations for trial sample size**
43

44
45 132 This study is based on the registered clinical trial study "Neo-adjuvant SABR for IVC Tumor Thrombus
46
47 133 in Newly Diagnosed RCC"^[15] retrieved on the Clinical trial website. The study sample size is two groups
48
49 134 with 15 cases in each group. In our study, there is only one intervention group. The study will be
50
51 135 conducted after the intervention. The focus is on the safety of the trial. The sample size is estimated to
52
53 136 be 20 cases.
54
55
56
57
58
59
60

137 Treatment and follow up

138 20 patients enrolled from outpatient service of Peking University Third Hospital in the intervention
139 group are treated with preoperative SABR to assist surgery. A total radiation dose of 30 Gy with 5
140 fractions will be given to IVC of each patient.

141 Simulation before radiotherapy will start on day 1. The subject lies on his back with hands at his sides.

142 The fixation technology of the negative pressure vacuum bag is utilized to fix his head, body, and limbs

143 simultaneously with a foot pedal. Using CT, MRI, and PET-CT to scan the upper boundary of the tumor

144 ≥ 15 cm upward, and the lower boundary ≥ 15 cm as the scanning range. CT images include unenhanced

145 phase (as the reference image), arterial phase, and venous phase with a slice thickness of 1-1.5mm. MRI

146 images include T1WI, T2WI, enhanced and DWI phases with a slice thickness of 1-3mm. Target

147 delineation will start on day 2. CT, MRI, and PET-CT fusion will be performed, with CT unenhanced

148 phase as the reference image to delineate the target area. Delineating vena cava tumor thrombus as gross

149 tumor volume (GTV) and stomach, duodenum, jejunum, ileum, colon, spinal cord, liver, esophagus as

150 organs at risk (OAR). The planning target volume (PTV) is generated by adding a 3mm margin around

151 the GTV. On day 3, a prescription dose of PTV 30Gy/5Gy/6f is designed by a senior medical physicist

152 and approved by an expert. This prescription then will be uploaded to Accuray MultiPlan® (Accuray

153 Inc., Sunnyvale, CA) treatment planning system. On day 4, cyberknife (CyberKnife® VSI™, Accuray

154 Inc., Sunnyvale, CA) radiotherapy will be carried out following the radiotherapy plan after the treatment

155 list signed and confirmed by the radiotherapist in charge and the planning physicist. Two or more

156 therapists will perform the radiotherapy. During the first treatment, the radiotherapist and physicist will

157 jointly participate in the location verification.

158 After 4-6 weeks of rest, re-admission to finish blood routine, blood biochemistry, coagulation function,

159 urine routine, enhanced CT of the urinary system, enhanced MRI of inferior vena cava on re-admission

160 day 1. Complete pre-operation preparations on re-admission day 3. Radical nephrectomy + IVC

161 thrombectomy will be performed on re-admission day 4.

162 Post-surgery visits at 1, 2, 3, 7 days and the day leaving hospital and 3, 6, 9, 12 months after the date of

1
2
3 163 radical nephrectomy and IVC thrombectomy include blood routine, blood biochemistry, erythrocyte
4
5 164 sedimentation rate, coagulation function, and urine routine.
6

7 165 Subjects will receive regular phone calls from the investigators to complete follow-up.
8

9 166 A SPIRIT figure of detailed flowchart for minimum assessments during the treatment and follow-up
10
11 167 phase is shown in Figure 1. A schematic outline of the treatment plan is shown in Figure 2.
12
13

14 168 **Adverse events**

15

16
17 169 Adverse events (AEs) for radiation and surgery will be collected respectively.
18

19 170 SABR-related AEs are defined using Common Terminology Criteria for Adverse Events (CTCAE) v4.0.
20

21 171 We are interested in acute and late toxicity including nausea, fatigue, anorexia, diarrhea, enteritis,
22
23 172 gastritis, fistula, dermatitis, anemia, lymphopenia, neutropenia, thrombocytopenia, and ALT/AST
24
25 173 elevation. Severe toxicity is defined as grade III-IV toxicity according to CTCAE v4.0.
26

27 174 Modified Clavien classification system^[16] is used to evaluate adverse events in terms of surgery.
28

29 175 Surgical AEs of interest are postoperative active bleeding, postoperative anemia, wound infection,
30
31 176 pulmonary infection, lower extremity deep vein thrombosis, pulmonary embolism, chylous fistula, renal
32
33 177 dysfunction, hyperkalemia, and continuous venovenous hemodiafiltration.
34

35 178 If any serious adverse event or important adverse event occurs, regardless of whether it is related to the
36
37 179 research intervention, or whether the intervention has been implemented, the investigator must be
38
39 180 notified by telephone/fax within 24 hours of the occurrence.
40
41

42 181 **Data analysis**

43

44
45 182 The enumeration data are described by case number and percentage, and chi square test is used. Rank
46
47 183 sum test is used to compare the rank data. The measurement data are expressed by means + standard
48
49 184 deviation. If the measurement data conform to normal distribution, independent sample t-test or analysis
50
51 185 of variance is used. The Kaplan-Meier method will be used to calculate the tumor-free rate, tumor-
52
53 186 specific survival rate, and overall survival rate with SPSS 18.0 software, and the Log-rank test will be
54
55 187 performed. The comparability of data and the comparison of short-term efficacy before and after the
56
57

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

191 **Ethics and dissemination**

192 **Ethics, informed consent and safety**

193 The trial protocol and the informed consent of the subjects were submitted and approved by the Peking
194 University Biomedical Ethics Committee. The written informed consent form will be obtained from all
195 individual participants in the study. The specific contents of the informed consent form are provided in
196 the supplementary materials. If the protocol is revised, only the corresponding revised part and the
197 revised informed consent form (if any) can be implemented after being reviewed and approved by the
198 ethics committee, and a copy of the approval of the Peking University Biomedical Ethics Committee is
199 required to be provided to the clinical monitor. If the revision of the protocol aims to reduce the clear
200 risk of the subjects, it can be implemented immediately, but it must be submitted to the relevant
201 departments and the ethics committee for a record as soon as possible.

202 **Confidentiality**

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

209 **Trial organization**

210 Our study is an investigator-initiated trial. The sponsor is Peking University, a Chinese government-

1
2
3 211 funded university. This study is conducted in the urology ward and oncology radiotherapy ward of
4
5 212 Peking University Third Hospital.
6
7

8 213 **Data entry**

9

10
11 214 According to the original observation records of the subjects, the researchers will load the data into the
12
13 215 case report form timely, completely, correctly and clearly. The questionnaire reviewed and signed by
14
15 216 the supervisor should be sent to the clinical research data administrator in time.
16

17 217 The corresponding database system will be used to input the data by two persons and two computers,
18
19 218 and then the database will be compared twice. If any problem is found during the period, the inspector
20
21 219 will be informed in time and the researcher will answer. The exchange of questions and answers should
22
23 220 be in the form of question list, which should be kept for future reference.
24
25

26 221 **Contents and methods of data verification and management**

27

28
29 222 After all case report forms have been double-entered and verified, the data manager will write a database
30
31 223 inspection report, which includes the completion of the study (including the list of dropped subjects),
32
33 224 selection/exclusion criteria check, completeness check, and logic consistency check, outlier data check,
34
35 225 time window check, combined medication check, adverse event check, etc.
36

37 226 At the review meeting, the main researchers, monitors, data administrators, and statisticians make
38
39 227 decisions on the subjects' informed consent and issues raised in the database inspection report, and write
40
41 228 a review report. The database will be locked at the same time.
42

43 229 To promote participant retention and complete follow-up, researchers should do a good job of subject
44
45 230 compliance education during the process of informed consent and follow-up.
46
47

48 231 **Data storage**

49

50
51
52 232 After completing the data entry and verification as required, the case report form will be archived and
53
54 233 stored in the order of numbers, and filled with a search catalog for future reference. Electronic data files
55
56 234 include databases, inspection procedures, analysis procedures, analysis results, codebooks, and
57
58

235 description files, etc., which will be stored in categories, and multiple backups will be stored on different
236 disks or recording media, and they will be stored properly to prevent damage. All original archives will
237 be kept within the corresponding period.

238 **Protocol amendments**

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

242 **Quality Control**

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

249 The specific supervision contents are as follows:

- 250 (1) The research plan is submitted to the ethics committee for approval.
- 251 (2) Participants in this study carefully implement the standard operating procedures for clinical
252 verification before, during and after verification.
- 253 (3) During the research process, the inspectors from the clinical trial research unit and the implementer
254 monitor the correctness and completeness of the data in the CRF.
- 255 (4) Researchers must undergo unified training, unified recording methods and judgment standards.
- 256 (5) The investigator will fill in the case report form according to the requirements, truthfully, in detail,
257 and carefully record the contents of the CRF to ensure that the content of the case report form is true
258 and reliable.
- 259 (6) All observations and findings in clinical research will be verified to ensure that the conclusions in

260 the clinical verification are derived from the original data, and there are corresponding data management
261 measures in the clinical verification and data processing.

262 **Stopping guidelines**

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

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

265 (2) The treatment effect of the experimental program is too poor, or even ineffective, and has no clinical
266 value.

267 (3) There are major mistakes in the clinical trial protocol or serious deviations in the implementation,
268 and it is difficult to evaluate the therapeutic effect.

269 (4) The applicant requests to terminate the experiment or the administrative department requests to
270 terminate the experiment.

271 **Discussion**

272 This study aims to evaluate the safety of the treatment by the study of preoperative stereotactic
273 radiotherapy combined with surgical treatment of patients with renal cell carcinoma and inferior vena
274 cava tumor thrombus.

275 Preoperative radiotherapy has been proven effective in many tumors, including rectal cancer,
276 esophageal cancer, and soft tissue sarcoma. Taking rectal cancer as an example, compared with surgery
277 alone, the effects of preoperative radiotherapy are mainly reflected in ①Reducing clinical staging and
278 increasing surgical resection rate^[17]. ②Increasing anus preservation rate and improving patients'
279 quality of life^[18]. ③Reducing local recurrence rate and improving long-term survival rate^[19]. However,
280 the understanding of the effects of renal cancer radiotherapy has undergone a torturous process. In the
281 past sixty years, the radiotherapy community has conducted high-quality randomized controlled studies,
282 including preoperative radiotherapy, postoperative radiotherapy, and intraoperative radiotherapy for
283 renal cancer. Unfortunately, the conclusions of most studies show that radiotherapy does not improve

1
2
3 284 the efficacy, and in some cases, it reduces the efficacy as well^[20-22]. Coupled with the later
4
5 285 radiobiological studies suggesting that renal cancer is not sensitive to conventionally fractionated
6
7 286 radiotherapy^[23], the research on renal cancer radiotherapy has fallen into a trough. In fact, in historical
8
9 287 research, the backwardness of technology has led to insufficient doses. The prescribed doses given to
10
11 288 tumors do not meet the standards for radical treatment^[24]. At the same time, normal tissues are not well
12
13 289 protected, including the duodenum and liver, which have been exposed to excessive radiation.

14
15 290 SABR, also known as stereotactic body radiotherapy (SBRT), uses high-precision radiotherapy
16
17 291 technology to focus the radical radiation dose (single dose > 8-10 Gy) to the tumor site through external
18
19 292 irradiation to achieve the purpose of radical treatment of the tumor. It has the characteristics of high
20
21 293 precision, high dose, high conformability, and low treatment frequency. It has been gradually used in
22
23 294 the treatment of solid tumors such as liver cancer, lung cancer, and spinal tumors in recent years, with
24
25 295 definite curative effect^[25]. SABR was firstly clinically applied for stage I non-small cell lung carcinoma,
26
27 296 and related literature reports that the long-term local tumor control rate can reach 90%^[26].

28
29 297 In the existing researches on the treatment of renal cell carcinoma with SABR, the separated fractions
30
31 298 and radiation doses are different. A study^[12] found that the SABR regimen with 4 fractions and a total
32
33 299 radiation dose of 48 Gy has no significant dose-related adverse reactions, which is safe and feasible for
34
35 300 patients with localized renal cell carcinoma. Another study^[9] recommended using 5 fractions and a total
36
37 301 radiation dose of 35Gy to treat patients with inoperable metastatic renal cancer. Most SABR protocols
38
39 302 often use 3 to 5 fractions^[27,28]. We choose tumor thrombus as the target organ of radiotherapy, not
40
41 303 including renal cancer tissue, to avoid the difficulty of surgical separation of the kidney due to edema,
42
43 304 fibrosis, or other reasons after irradiation. Since the growth level of the tumor thrombus usually
44
45 305 coincides with the horizontal part of the duodenum, the duodenal perforation will happen if the radical
46
47 306 dose of the tumor thrombus is taken. Based on the results of existing studies and to limit organ toxicity,
48
49 307 our trial design adopts a more conservative total radiation dose - 30Gy with 5 fractions.

50
51 308 Considering that the hyperemia and edema^[29,30] of tumor-adjacent tissues in a short time after
52
53 309 radiotherapy may increase the risk of surgery, we decide to operate 6-8 weeks after radiotherapy. At
54
55 310 that time, the peritumoral edema will be reduced, and the tumor will not continue to grow due to too

1
2
3 311 long delay.
4
5 312 The clinical significances of this trial are as follows: ①For Mayo III-IV classification, it may reduce
6
7 313 the difficulty of operation, blood loss, blood transfusion rate, and perioperative complications. ②For
8
9 314 Mayo II-IV classification, preoperative radiotherapy + surgery may be better than surgery alone, which
10
11 315 prolongs survival and reduces recurrence rate. ③When the tumor thrombus invades the inferior vena
12
13 316 cava wall in a wide range, preoperative radiotherapy can be used to preserve the inferior vena cava
14
15 317 vessel wall.

16
17
18 318 The pathological changes of tumors after radiotherapy have been proved to have prognostic significance
19
20 319 in other tumors^[17,31]. Tumors such as rectal cancer have clear grading standards, which are divided into
21
22 320 4 grades according to the degree of residual tumor after radiotherapy. Different grades correspond to
23
24 321 different prognoses. So far, this study is the only preoperative radiotherapy study in the world that
25
26 322 focuses on tumor thrombus, and is also a pioneering study on the prognostic value of pathological
27
28 323 changes after radiotherapy. Therefore, this study attempts to initially explore the post-radiotherapy
29
30 324 changes of renal tumor thrombus, and judge the prognosis of the tumor according to the different
31
32 325 pathological changes.

33
34 326 We hope to collect possible treatment data for a further large trial by this study.

35 36 37 327 **Trial Status**

38
39
40 328 Protocol version number: 2018-04-17. V2.30.

41
42 329 Recruitment began on 2018-05-01 and will be completed in 2021-12.

43 44 45 330 **Abbreviations**

46
47
48 331 AEs: adverse events; CRF: case report form; CTCAE: Common Terminology Criteria Adverse Events;
49
50 332 ECOG: Eastern Cooperative Oncology Group; GTV: gross tumor volume; IVCTT: inferior vena cava
51
52 333 tumor thrombus; OAR: organs at risk; PTV: planning target volume; RCC: Renal cell carcinoma; RFS:
53
54 334 Recurrent-free survival; SABR: stereotactic ablative body radiotherapy; SBRT: stereotactic body
55
56 335 radiotherapy

1
2
3 **336 Declarations**

4
5
6
7 **337 Patient and Public Involvement**

8
9
10 **338** Patients or the public will not be involved in the design, or conduct, or reporting, or dissemination plans
11
12 **339** of our research.

13
14
15 **340 Consent for publication**

16
17
18 **341** Not applicable.

19
20
21 **342 Availability of data and materials**

22
23
24 **343** Researchers, monitors and reviewers of ethics committees will have access to the final trial dataset.

25
26
27 **344 Dissemination policy**

28
29
30 **345** Investigators and sponsor will communicate trial results to participants, healthcare professionals, the
31
32 **346** public, and other relevant groups via publication. The public will access to the full protocol, participant-
33
34 **347** level dataset, and statistical code from online database. Professional medical writers will complete an
35
36 **348** article of this trial.

37
38
39 **349 Authors' contributions**

40
41
42 **350** Project development: ZL, RP, JW, HW, LM; Wrote study protocol: YL, ZL, RP, RX; Wrote this
43
44 **351** manuscript: YL, ZL, RP; All authors have read and approved this manuscript, and ensure that this is the
45
46 **352** case.

47
48
49 **353 Funding statement**

50
51
52 **354** This work was supported by Peking University. The costs incurred in the research process are derived
53
54 **355** from the following funding: Project No. BMU2017YS001-2, which is detailed as the “Double First-
55
56
57

356 Class” Advantage Discipline Construction Project of Peking University.

357 **Competing interests statement**

358 The authors declare that they have no competing interests.

359 **Acknowledgements**

360 The authors thank the entire staff of the Department of Urology and Department of Radiation Oncology,
361 Peking University Third Hospital.

362 **References**

- 363 [1] Padala SA, Barsouk A, Thandra KC, et al. Epidemiology of Renal Cell Carcinoma[J]. *World J Oncol*,
364 2020, 11(3): 79-87. doi: 10.14740/wjon1279
- 365 [2] Fusco V, Parisi S, d'Andrea B, et al. Role of radiotherapy in the treatment of renal cell cancer:
366 updated and critical review[J]. *Tumori*, 2017, 103(6): 504-510. doi: 10.5301/tj.5000640
- 367 [3] Blute ML, Leibovich BC, Lohse CM, et al. The Mayo Clinic experience with surgical management,
368 complications and outcome for patients with renal cell carcinoma and venous tumour thrombus[J].
369 *BJU Int*, 2004, 94(1): 33-41. doi: 10.1111/j.1464-410X.2004.04897.x
- 370 [4] Lawindy SM, Kurian T, Kim T, et al. Important surgical considerations in the management of renal
371 cell carcinoma (RCC) with inferior vena cava (IVC) tumour thrombus[J]. *BJU Int*, 2012, 110(7):
372 926-939. doi: 10.1111/j.1464-410X.2012.11174.x
- 373 [5] Ljungberg B, Cowan NC, Hanbury DC, et al. EAU guidelines on renal cell carcinoma: the 2010
374 update[J]. *Eur Urol*, 2010, 58(3): 398-406. doi: 10.1016/j.eururo.2010.06.032
- 375 [6] Al Otaibi M, Abou Youssif T, Alkhalidi A, et al. Renal cell carcinoma with inferior vena caval
376 extention: impact of tumour extent on surgical outcome[J]. *BJU Int*, 2009, 104(10): 1467-1470. doi:
377 10.1111/j.1464-410X.2009.08575.x
- 378 [7] Jibiki M, Iwai T, Inoue Y, et al. Surgical strategy for treating renal cell carcinoma with thrombus
379 extending into the inferior vena cava[J]. *J Vasc Surg*, 2004, 39(4): 829-835. doi:
380 10.1016/j.jvs.2003.12.004
- 381 [8] Singh AK, Winslow TB, Kermany MH, et al. A Pilot Study of Stereotactic Body Radiation Therapy
382 Combined with Cytoreductive Nephrectomy for Metastatic Renal Cell Carcinoma[J]. *Clin Cancer*
383 *Res*, 2017, 23(17): 5055-5065. doi: 10.1158/1078-0432.Ccr-16-2946
- 384 [9] Correa RJM, Ahmad B, Warner A, et al. A prospective phase I dose-escalation trial of stereotactic
385 ablative radiotherapy (SABR) as an alternative to cytoreductive nephrectomy for inoperable patients
386 with metastatic renal cell carcinoma[J]. *Radiat Oncol*, 2018, 13(1): 47. doi: 10.1186/s13014-018-
387 0992-3
- 388 [10] Teh B, Bloch C, Galli-Guevara M, et al. The treatment of primary and metastatic renal cell
389 carcinoma (RCC) with image-guided stereotactic body radiation therapy (SBRT)[J]. *Biomed*
390 *Imaging Interv J*, 2007, 3(1): e6. doi: 10.2349/bij.3.1.e6
- 391 [11] Siva S, Jackson P, Kron T, et al. Impact of stereotactic radiotherapy on kidney function in primary
392 renal cell carcinoma: Establishing a dose-response relationship[J]. *Radiother Oncol*, 2016, 118(3):
393 540-546. doi: 10.1016/j.radonc.2016.01.027
- 394 [12] Ponsky L, Lo SS, Zhang Y, et al. Phase I dose-escalation study of stereotactic body radiotherapy
395 (SBRT) for poor surgical candidates with localized renal cell carcinoma[J]. *Radiother Oncol*, 2015,
396 117(1): 183-187. doi: 10.1016/j.radonc.2015.08.030

- 1
2
3 397 [13] Svedman C, Sandström P, Pisa P, et al. A prospective Phase II trial of using extracranial stereotactic
4 398 radiotherapy in primary and metastatic renal cell carcinoma[J]. *Acta Oncol*, 2006, 45(7): 870-875.
5 399 doi: 10.1080/02841860600954875
- 6 400 [14] Hannan R, Margulis V, Chun SG, et al. Stereotactic radiation therapy of renal cancer inferior vena
7 401 cava tumor thrombus[J]. *Cancer Biol Ther*, 2015, 16(5): 657-661. doi:
8 402 10.1080/15384047.2015.1026506
- 9 403 [15] <https://clinicaltrials.gov/ct2/show/study/NCT02473536>.
- 10 404 [16] Mandal S, Sankhwar SN, Kathpalia R, et al. Grading complications after transurethral resection of
11 405 prostate using modified Clavien classification system and predicting complications using the
12 406 Charlson comorbidity index[J]. *Int Urol Nephrol*, 2013, 45(2): 347-354. doi: 10.1007/s11255-013-
13 407 0399-x
- 14 408 [17] Lim SB, Hong SM, Yu CS, et al. Prevalence and clinical significance of acellular mucin in locally
15 409 advanced rectal cancer patients showing pathologic complete response to preoperative
16 410 chemoradiotherapy[J]. *Am J Surg Pathol*, 2013, 37(1): 47-52. doi:
17 411 10.1097/PAS.0b013e3182657186
- 18 412 [18] Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for
19 413 rectal cancer[J]. *N Engl J Med*, 2004, 351(17): 1731-1740. doi: 10.1056/NEJMoa040694
- 20 414 [19] Kapiteijn E, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total
21 415 mesorectal excision for resectable rectal cancer[J]. *N Engl J Med*, 2001, 345(9): 638-646. doi:
22 416 10.1056/NEJMoa010580
- 23 417 [20] Kjaer M, Iversen P, Hvidt V, et al. A randomized trial of postoperative radiotherapy versus
24 418 observation in stage II and III renal adenocarcinoma. A study by the Copenhagen Renal Cancer
25 419 Study Group[J]. *Scand J Urol Nephrol*, 1987, 21(4): 285-289. doi: 10.3109/00365598709180784
- 26 420 [21] Juusela H, Malmio K, Alfthan O, et al. Preoperative irradiation in the treatment of renal
27 421 adenocarcinoma[J]. *Scand J Urol Nephrol*, 1977, 11(3): 277-281. doi: 10.3109/00365597709179965
- 28 422 [22] Gez E, Libes M, Bar-Deroma R, et al. Postoperative irradiation in localized renal cell carcinoma:
29 423 the Rambam Medical Center experience[J]. *Tumori*, 2002, 88(6): 500-502. doi:
30 424 10.1016/0360-3016(95)02029-2
- 31 425 [23] Deschavanne PJ, Fertil B. A review of human cell radiosensitivity in vitro[J]. *Int J Radiat Oncol*
32 426 *Biol Phys*, 1996, 34(1): 251-266. doi: 10.1016/0360-3016(95)02029-2
- 33 427 [24] Dengina N, Tsimafeyeu I, Mitin T. Current Role of Radiotherapy for Renal-Cell Carcinoma:
34 428 Review[J]. *Clin Genitourin Cancer*, 2017, 15(2): 183-187. doi: 10.1016/j.clgc.2016.09.004
- 35 429 [25] Lo SS, Slotman BJ, Lock M, et al. The development of stereotactic body radiotherapy in the past
36 430 decade: a global perspective[J]. *Future Oncol*, 2015, 11(19): 2721-2733. doi: 10.2217/fon.15.220
- 37 431 [26] Kann BH, Miccio JA, Stahl JM, et al. Stereotactic body radiotherapy with adjuvant systemic therapy
38 432 for early-stage non-small cell lung carcinoma: A multi-institutional analysis[J]. *Radiother Oncol*,
39 433 2019, 132: 188-196. doi: 10.1016/j.radonc.2018.10.017
- 40 434 [27] Siva S, Louie AV, Warner A, et al. Pooled analysis of stereotactic ablative radiotherapy for primary
41 435 renal cell carcinoma: A report from the International Radiosurgery Oncology Consortium for
42 436 Kidney (IROCK)[J]. *Cancer*, 2018, 124(5): 934-942. doi: 10.1002/cncr.31156
- 43 437 [28] Siva S, Ellis RJ, Ponsky L, et al. Consensus statement from the International Radiosurgery Oncology
44 438 Consortium for Kidney for primary renal cell carcinoma[J]. *Future Oncol*, 2016, 12(5): 637-645.
45 439 doi: 10.2217/fon.16.2
- 46 440 [29] Li Y, Lin J, Xiao J, et al. Therapeutic effects of Co-Venenum Bufonis Oral Liquid on radiation-
47 441 induced esophagitis in rats[J]. *Exp Anim*, 2020, 69(3): 354-362. doi: 10.1538/expanim.19-0142
- 48 442 [30] Lee SR, Yang KA, Kim SK, et al. Radiation-induced intratumoral necrosis and peritumoral edema
49 443 after gamma knife radiosurgery for intracranial meningiomas[J]. *J Korean Neurosurg Soc*, 2012,
50 444 52(2): 98-102. doi: 10.3340/jkns.2012.52.2.98
- 51 445 [31] Chirieac LR, Swisher SG, Correa AM, et al. Signet-ring cell or mucinous histology after
52 446 preoperative chemoradiation and survival in patients with esophageal or esophagogastric junction
53 447 adenocarcinoma[J]. *Clin Cancer Res*, 2005, 11(6): 2229-2236. doi: 10.1158/1078-0432.Ccr-04-
54 1840

	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
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)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

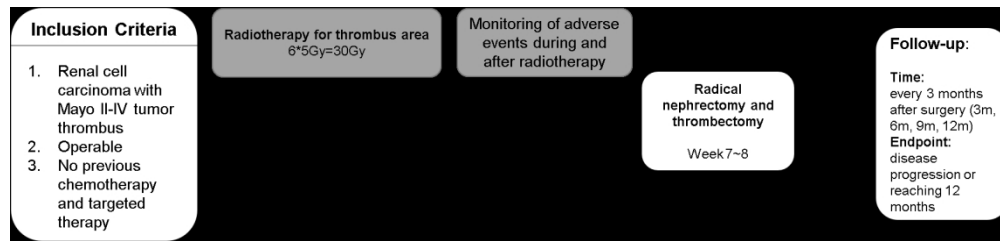


Figure 2. Schematic outline of the treatment plan. Patients with renal cell carcinoma with Mayo II-IV tumor thrombus will finish radiotherapy for thrombus area (total 30Gy). Radical nephrectomy and thrombectomy will be performed between week 7~8. Follow up for secondary endpoints will be starting at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

314x73mm (150 x 150 DPI)



SPIRIT 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.

1			
2		11d	N/A. Not covered in our trial.
3			
4	Outcomes	12	Line 109-130
5			
6	Participant	13	Figure 1&2.
7	timeline		
8			
9	Sample size	14	Line 131-136
10			
11	Recruitment	15	Line 138-140
12			

Methods: Assignment of interventions (for controlled trials)

Allocation:

16	Sequence	16a	N/A. This is not a controlled trial.
17	generation		
18			
19			
20	Allocation	16b	N/A. This is not a controlled trial.
21	concealment		
22	mechanism		
23			
24	Implementation	16c	N/A. This is not a controlled trial.
25			
26	Blinding	17a	N/A. This is not a controlled trial.
27	(masking)		
28			
29		17b	N/A. This is not a controlled trial.
30			

Methods: Data collection, management, and analysis

33	Data collection	18a	Line 213-228
34	methods		
35			
36		18b	Line 229-230
37			
38	Data	19	Line 231-237
39	management		
40			
41			
42	Statistical	20a	Line 182-188
43	methods		
44			
45		20b	N/A. There are no additional analyses due to small sample size.
46			
47		20c	Line 189-190
48			

Methods: Monitoring

51	Data monitoring	21a	Line 242-261
52			
53		21b	Line 262-270
54			
55	Harms	22	Line 168-180
56			
57	Auditing	23	Line 243-246
58			

Ethics and dissemination

1			
2	Research ethics	24	Line 192-201
3	approval		
4			
5	Protocol	25	Line 238-241
6	amendments		
7			
8	Consent or assent	26a	Line 193-196
9			
10		26b	N/A. Participant data and biological specimens will not be used in
11			ancillary studies.
12			
13	Confidentiality	27	Line 202-208
14			
15	Declaration of	28	Line 358
16	interests		
17			
18	Access to data	29	Line 343
19			
20	Ancillary and	30	N/A. There is no compensation to those who suffer harm from trial
21	post-trial care		participation except medical care.
22			
23	Dissemination	31a	Line 345-348
24	policy		
25			
26		31b	Line 345-348
27			
28		31c	Line 345-348
29			
30			
31	Appendices		
32			
33	Informed consent	32	Line 193-196
34	materials		
35			
36	Biological	33	N/A. No biological specimens will be used for genetic or molecular
37	specimens		analysis.
38			

*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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" 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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-055364.R1
Article Type:	Protocol
Date Submitted by the Author:	16-Dec-2021
Complete List of Authors:	Liu, Yunchong; Peking University Third Hospital, Liu, Zhuo; Peking University Third Hospital, Department of Urology Peng, Ran; Peking University Third Hospital, Department of Radiation Oncology Xiao, Ruotao; Peking University Third Hospital, Department of Urology Wang, Junjie; Peking University Third Hospital, Department of Radiation Oncology Wang, Hao; Peking University Third Hospital, Department of Radiation Oncology Ma, Lulin; Peking University Third Hospital, Department of Urology
Primary Subject Heading:	Urology
Secondary Subject Heading:	Radiology and imaging
Keywords:	RADIOTHERAPY, Urological tumours < UROLOGY, Kidney tumours < ONCOLOGY

SCHOLARONE™
Manuscripts

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

1 Yunchong Liu^{1†}, Zhuo Liu^{1†}, Ran Peng^{2†}, Ruotao Xiao¹, Junjie Wang², Hao Wang^{2*} and
2 Lulin Ma^{1*}

3 ¹Department of Urology, Peking University Third Hospital, Beijing 100191, China.

4 ²Department of Radiation Oncology, Peking University Third Hospital, Beijing 100191, China.

5 [†]Yunchong Liu, Zhuo Liu, and Ran Peng contributed equally to this work.

6 *Correspondence: hhbysy@126.com; malulinpku@163.com

7 Abstract

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

13 **Methods and analysis:**

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

15 **Study treatment:** Preoperative stereotactic ablative radiotherapy combined with surgical treatment.

16 **Primary endpoint:** (1) Adverse reactions after 4-6 weeks of SABR and after operation.

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

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

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

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

26 **Planned sample size:** 20 patients.

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

29 **Trial registration:** ChiCTR1800015118. Clinical trials on the safety and effectiveness of neoadjuvant
30 stereotactic radiotherapy combined with surgical treatment for patients with renal cell carcinoma with
31 inferior vena cava tumor thrombus. Registered 08 March 2018,
32 <http://www.chictr.org.cn/showproj.aspx?proj=25747>

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

35 **Strengths and limitations of this study**

36 Strengths

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

39 limitations

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

42 Introduction

43 Renal cell carcinoma (RCC) is a common malignant tumor of the urinary system and accounts for 2~3%
44 of adult malignant tumors^[1]. Nearly 1/3 of the patients on presentation are locally advanced tumors
45 (2010 AJCC renal cancer stage III or IV) at the time of diagnosis^[2]. RCC has a tendency for venous
46 invasion and 4% to 10% of newly diagnosed cases have inferior vena cava tumor thrombus (IVCTT)^[3].
47 Currently, the traditional treatment used for RCC combined with IVCTT is surgery. Commonly used
48 surgical methods are open or laparoscopic radical nephrectomy + IVC thrombectomy^[4,5], which have a
49 high risk and require extremely proficient operating skills and surgical capabilities of the doctor^[6-8].
50 Open or laparoscopic surgery may have early postoperative complications, such as bleeding, lung
51 infection, deep vein thrombosis of the lower limbs, pulmonary embolism, renal failure, liver failure,
52 urinary fistula, chylous fistula, and so on. Severe complications can even lead to death^[3].
53 At present, the main problems in the treatment of RCC combined with IVCTT can be summarized in
54 the following aspects: ① The operation is with high difficulties, risks, and many complications^[3]. ②
55 For Mayo I -IV grade, radical nephrectomy + IVC thrombectomy can improve the 5-year survival rate
56 of patients, but it can only reach 40%-60%^[9]. How to further improve the survival rate of patients is a
57 hot research topic. ③ When the tumor thrombus invades the inferior vena cava wall in a wide range,
58 segmental resection of the inferior vena cava is required^[10]. Lower limb edema and renal insufficiency
59 may occur after surgery.
60 Nowadays, the equipment, technology, and concept of radiotherapy have ushered in a leap-forward
61 development. The development of intensity-modulated radiotherapy technology has allowed tumors and
62 surrounding normal tissues to obtain completely different doses. Image-guided technology allows the
63 doses given from the radiotherapy plan to hit the tumor accurately. Stereotactic ablative body
64 radiotherapy (SABR) has greatly expanded and partially subverted the understanding of traditional
65 radiobiology^[11]. In the past 10 years, new explorations of renal cancer have been continuously reported,
66 mainly confined to inoperable renal cancer patients, all using SABR technology, and its local control

67 rate and survival rate have reached a high level^[12-17]. Many phase-II SABR clinical trials for renal cell
68 carcinoma are ongoing (NCT02141919, NCT01890590, NCT02613819, NCT03747133, and
69 NCT03108703). Combined with the good results achieved by the SABR technique in inoperable renal
70 cancer patients, we expect that it can shrink and reduce the level of tumor thrombus, increase surgical
71 resection rate, and reduce surgical risk. Evidence has shown that SABR can reduce the transverse
72 diameter of the tumor thrombus^[18], which may help solve the problem of venous obstruction by tumor
73 thrombus. And the team's long-term follow-up results of two cases showed that SABR to RCC with
74 IVCTT could get good local tumor control in selected patients^[19]. Its safety and effectiveness need to
75 be further examined.

76 **Aims**

77 To determine the safety of the treatment by the study of preoperative stereotactic radiotherapy combined
78 with surgical treatment of patients with renal cell carcinoma and inferior vena cava tumor thrombus.
79 Main purpose: 1. To identify the acute and late toxicity of radiotherapy. Severe toxicity is defined as
80 grade III-IV toxicity according to Common Terminology Criteria Adverse Events (CTCAE) v4.0. 2.
81 Secondary purpose: To identify whether the difficulty or risk of surgery is increased after radiotherapy
82 by analyzing perioperative complications, operation time, intraoperative bleeding volume,
83 intraoperative transfusion volume of suspended red blood cells, and postoperative hospital stay. Using
84 the follow-up data of the patients to clarify the curative effect of the treatment: 1. For Mayo III-IV
85 classification, it may reduce the difficulty of operation, blood loss, blood transfusion rate and
86 perioperative complications. 2. For Mayo II-IV classification, preoperative radiotherapy + surgery may
87 be better than surgery alone, which prolongs survival and reduces recurrence rate. 3. When the tumor
88 thrombus invades the inferior vena cava wall in a wide range, preoperative radiotherapy can be used to
89 preserve the inferior vena cava vessel wall.

90 **Methods and Analysis**

91 **Study design**

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

93 **Inclusion criteria**

94 (1) Age \geq 18 years old.

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

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

97 (4) Subjects eligible for SABR for IVC tumor thrombosis at the decision of the radiation oncologist.

98 (5) Subjects eligible for radical nephrectomy and inferior vena cava thrombectomy at the decision
99 of urologists.

100 (6) ECOG 0-2.

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

102 **Exclusion criteria**

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

105 (2) Subjects with a history of preoperative targeted therapy, preoperative chemotherapy, or other
106 related treatments.

107 (3) Subjects with a history of pulmonary embolism.

108 (4) Subjects with severe cardiopulmonary insufficiency, severe arrhythmia, myocardial infarction,
109 angina pectoris, severe coagulation disease, or severe liver disease that cannot tolerate SABR or surgery.

110 (5) Subjects with diseases that severely affect the judgment of patients, such as mental disorders.

1
2
3 111 **Endpoints**
4

5
6 112 *Primary endpoint*
7

8
9 113 (1) Adverse reactions after 4-6 weeks of SABR and after operation. Measurement time point: 4-6
10 114 weeks after SABR treatment and after operation. Measurement method: observation and inspection.
11

12
13
14 115 *Secondary endpoints*
15

16
17 116 (1) Perioperative indicators including operation time, intraoperative bleeding volume, and
18 117 postoperative complications. Measurement time point: postoperative. Measurement method: surgical
19 118 record or observation and inspection.
20

21
22 119 (2) Mayo staging of tumor thrombus. Measurement time point: before and after radiotherapy.
23 120 Measurement method: CT or MRI.
24

25
26 121 (3) The length of the tumor thrombus from the corresponding anatomical mark. Measurement time
27 122 point: before and after radiotherapy. Measurement method: CT or MRI.
28

29
30 123 (4) Invasion of the inferior vena cava wall. Measurement time point: before and after radiotherapy.
31 124 Measurement method: CT or MRI.
32

33
34 125 (5) The longest diameter of the tumor. Measurement time point: before and after radiotherapy.
35 126 Measurement method: CT or MRI.
36

37
38 127 (6) Lymph node condition. Measurement time point: before and after radiotherapy. Measurement
39 128 method: CT or MRI.
40

41
42 129 (7) Recurrent-free survival (RFS) rate of the tumor. Measurement time point: postoperative.
43 130 Measurement method: CT or MRI, follow-up.
44

45
46 131 (8) Cancer-specific survival rate. Measurement time point: postoperative. Measurement method:
47 132 follow-up.
48

49
50 133 (9) Overall survival rate. Measurement time point: postoperative. Measurement method: follow-up.
51
52
53
54
55
56
57
58
59
60

1
2
3 **134 Statistical calculations for trial sample size**
4
5

6 **135** This study is based on the registered clinical trial study "Neo-adjuvant SABR for IVC Tumor Thrombus
7
8 **136** in Newly Diagnosed RCC"^[20] retrieved on the Clinical trial website. It's a single-arm study and the
9
10 **137** sample size is 6 for lead-in phase and 23 for phase II. In our study, there is only one intervention group.
11
12 **138** The study will be conducted after the intervention. The focus is on the safety of the trial. The sample
13
14 **139** size is estimated to be 20 cases.
15

16
17 **140 Treatment and follow up**
18

19
20 **141** 20 patients enrolled from outpatient service of Peking University Third Hospital in the intervention
21
22 **142** group are treated with preoperative SABR to assist surgery. A total radiation dose of 30 Gy with 5
23
24 **143** fractions will be given to IVC of each patient.
25

26 **144** Simulation before radiotherapy will start on day 1. The subject lies on his back with hands at his sides.
27
28 **145** The fixation technology of the negative pressure vacuum bag is utilized to fix his head, body, and limbs
29
30 **146** simultaneously with a foot pedal. Using CT, MRI, and PET-CT to scan the upper boundary of the tumor
31
32 **147** ≥ 15 cm upward, and the lower boundary ≥ 15 cm as the scanning range. CT images include unenhanced
33
34 **148** phase (as the reference image), arterial phase, and venous phase with a slice thickness of 1-1.5mm. MRI
35
36 **149** images include T1WI, T2WI, enhanced and DWI phases with a slice thickness of 1-3mm. Target
37
38 **150** delineation will start on day 2. CT, MRI, and PET-CT fusion will be performed, with CT unenhanced
39
40 **151** phase as the reference image to delineate the target area. Delineating vena cava tumor thrombus as gross
41
42 **152** tumor volume (GTV) and stomach, duodenum, jejunum, ileum, colon, spinal cord, liver, esophagus as
43
44 **153** organs at risk (OAR). The planning target volume (PTV) is generated by adding a 3mm margin around
45
46 **154** the GTV. On day 3, a prescription dose of PTV 30Gy/5Gy/6f over 1 week is designed by a senior
47
48 **155** medical physicist and approved by an expert. This prescription then will be uploaded to Accuray
49
50 **156** MultiPlan® (Accuray Inc., Sunnyvale, CA) treatment planning system. On day 4, cyberknife
51
52 **157** (CyberKnife® VSI™, Accuray Inc., Sunnyvale, CA) radiotherapy will be carried out following the
53
54 **158** radiotherapy plan after the treatment list signed and confirmed by the radiotherapist in charge and the
55
56
57
58
59
60

1
2
3 159 planning physicist. Two or more therapists will perform the radiotherapy. During the first treatment, the
4
5 160 radiotherapist and physicist will jointly participate in the location verification.
6

7 161 After 4-6 weeks of rest, re-admission to finish blood routine, blood biochemistry, coagulation function,
8
9 162 urine routine, enhanced CT of the urinary system, enhanced MRI of inferior vena cava on re-admission
10
11 163 day 1. Complete pre-operation preparations on re-admission day 3. Radical nephrectomy + IVC
12
13 164 thrombectomy will be performed on re-admission day 4.
14

15 165 Post-surgery visits at 1, 2, 3, 7 days and the day leaving hospital and 3, 6, 9, 12 months after the date of
16
17 166 radical nephrectomy and IVC thrombectomy include blood routine, blood biochemistry, erythrocyte
18
19 167 sedimentation rate, coagulation function, and urine routine.
20

21 168 Subjects will receive regular phone calls from the investigators to complete follow-up.
22

23 169 A SPIRIT figure of detailed flowchart for minimum assessments during the treatment and follow-up
24
25 170 phase is shown in Figure 1. A schematic outline of the treatment plan is shown in Figure 2.
26

27 28 171 **Adverse events**

29
30
31 172 Adverse events (AEs) for radiation and surgery will be collected respectively.
32

33 173 SABR-related AEs are defined using Common Terminology Criteria for Adverse Events (CTCAE) v4.0.
34

35 174 We are interested in acute and late toxicity including nausea, fatigue, anorexia, diarrhea, enteritis,
36
37 175 gastritis, fistula, dermatitis, anemia, lymphopenia, neutropenia, thrombocytopenia, and ALT/AST
38
39 176 elevation. Severe toxicity is defined as grade III-IV toxicity according to CTCAE v4.0.
40

41 177 Modified Clavien classification system^[21] is used to evaluate adverse events in terms of surgery.
42

43 178 Surgical AEs of interest are postoperative active bleeding, postoperative anemia, wound infection,
44
45 179 pulmonary infection, lower extremity deep vein thrombosis, pulmonary embolism, chylous fistula, renal
46
47 180 dysfunction, hyperkalemia, and continuous venovenous hemodiafiltration.
48

49 181 If any serious adverse event or important adverse event occurs, regardless of whether it is related to the
50
51 182 research intervention, or whether the intervention has been implemented, the investigator must be
52
53 183 notified by telephone/fax within 24 hours of the occurrence.
54
55
56
57
58
59
60

184 **Data analysis**

185 The enumeration data are described by case number and percentage, and chi square test is used. Rank
186 sum test is used to compare the rank data. The measurement data are expressed by means + standard
187 deviation. If the measurement data conform to normal distribution, independent sample t-test or analysis
188 of variance is used. The Kaplan-Meier method will be used to calculate the tumor-free rate, tumor-
189 specific survival rate, and overall survival rate with SPSS 18.0 software, and the Log-rank test will be
190 performed. The comparability of data and the comparison of short-term efficacy before and after the
191 test will be tested by Fisher's exact probability method. $P < 0.05$ is considered statistically significant.
192 Intention-to-treat analysis is used for the results of subjects who drop out, lost to follow-up or do not
193 complete the trial process. Multiple imputation is used for missing data.

194 **Ethics and dissemination**

195 **Ethics, informed consent and safety**

196 The trial protocol and the informed consent of the subjects were submitted and approved by the Peking
197 University Biomedical Ethics Committee. The written informed consent form will be obtained from all
198 individual participants in the study. The specific contents of the informed consent form are provided in
199 the supplementary materials. If the protocol is revised, only the corresponding revised part and the
200 revised informed consent form (if any) can be implemented after being reviewed and approved by the
201 ethics committee, and a copy of the approval of the Peking University Biomedical Ethics Committee is
202 required to be provided to the clinical monitor. If the revision of the protocol aims to reduce the clear
203 risk of the subjects, it can be implemented immediately, but it must be submitted to the relevant
204 departments and the ethics committee for a record as soon as possible.

205 **Confidentiality**

206 The data involved in the research process will be taken care of to protect the privacy of the subjects. For

207 example, the identification code table contains information such as the subject's name, phone number,
208 ID number, and home address. Researchers will keep it properly and take it out for inquiry when follow-
209 up is needed. In addition, the cover and information page of case report form (CRF) will record the
210 subject's initials rather than the signature of the name, and the informed consent signed by the subject
211 will be kept separately from other information to prevent the disclosure of the subject's information.

212 **Trial organization**

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

216 **Data entry**

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

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

224 **Contents and methods of data verification and management**

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

229 At the review meeting, the main researchers, monitors, data administrators, and statisticians make
230 decisions on the subjects' informed consent and issues raised in the database inspection report, and write

1
2
3 231 a review report. The database will be locked at the same time.

4
5 232 To promote participant retention and complete follow-up, researchers should do a good job of subject
6
7 233 compliance education during the process of informed consent and follow-up.
8
9

10 234 **Data storage**

11
12
13 235 After completing the data entry and verification as required, the case report form will be archived and
14
15 236 stored in the order of numbers, and filled with a search catalog for future reference. Electronic data files
16
17 237 include databases, inspection procedures, analysis procedures, analysis results, codebooks, and
18
19 238 description files, etc., which will be stored in categories, and multiple backups will be stored on different
20
21 239 disks or recording media, and they will be stored properly to prevent damage. All original archives will
22
23 240 be kept within the corresponding period.
24

25 26 241 **Protocol amendments**

27
28
29 242 When the supervisors find that the phenomenon of non-compliance with the inclusion criteria persists,
30
31 243 or the selection criteria are too strict, resulting in a low number of subjects, a supervision meeting will
32
33 244 be carried out to amend the protocol.
34

35 36 245 **Quality Control**

37
38
39 246 During the trial and research process, clinical monitors will be assigned to conduct regular on-site
40
41 247 supervision visits to the research to ensure that all the contents of the research plan are strictly followed
42
43 248 and the information filled in is correct. the process will be independent from investigators and the
44
45 249 sponsor. The test center shall objectively and truthfully record and retain all data and the execution and
46
47 250 modification of the program during the test and research process. During the recruitment phase, the
48
49 251 consistency of the selection/exclusion criteria will be ensured as much as possible.
50

51
52 252 The specific supervision contents are as follows:

53
54 253 (1) The research plan is submitted to the ethics committee for approval.

55
56 254 (2) Participants in this study carefully implement the standard operating procedures for clinical
57

1
2
3 255 verification before, during and after verification.
4

5 256 (3) During the research process, the inspectors from the clinical trial research unit and the implementer
6
7 257 monitor the correctness and completeness of the data in the CRF.
8

9 258 (4) Researchers must undergo unified training, unified recording methods and judgment standards.
10

11 259 (5) The investigator will fill in the case report form according to the requirements, truthfully, in detail,
12
13 260 and carefully record the contents of the CRF to ensure that the content of the case report form is true
14
15 261 and reliable.
16

17 262 (6) All observations and findings in clinical research will be verified to ensure that the conclusions in
18
19 263 the clinical verification are derived from the original data, and there are corresponding data management
20
21 264 measures in the clinical verification and data processing.
22

23 24 265 **Stopping guidelines**

25
26
27 266 The principles and treatment methods for early termination of the study, including:

28
29 267 (1) If serious safety problems are found in the trial, the clinical trial will be terminated in time.
30

31 268 (2) The treatment effect of the experimental program is too poor, or even ineffective, and has no clinical
32
33 269 value.
34

35 270 (3) There are major mistakes in the clinical trial protocol or serious deviations in the implementation,
36
37 271 and it is difficult to evaluate the therapeutic effect.
38

39 272 (4) The applicant requests to terminate the experiment or the administrative department requests to
40
41 273 terminate the experiment.
42
43

44 45 274 **Discussion**

46
47
48 275 This study aims to evaluate the safety of the treatment by the study of preoperative stereotactic
49
50 276 radiotherapy combined with surgical treatment of patients with renal cell carcinoma and inferior vena
51
52 277 cava tumor thrombus.
53

54
55 278 Preoperative radiotherapy has been proven effective in many tumors, including rectal cancer,
56
57

1
2
3 279 esophageal cancer, and soft tissue sarcoma. Taking rectal cancer as an example, compared with surgery
4
5 280 alone, the effects of preoperative radiotherapy are mainly reflected in ①Reducing clinical staging and
6
7 281 increasing surgical resection rate^[22]. ②Increasing anus preservation rate and improving patients'
8
9 282 quality of life^[23]. ③Reducing local recurrence rate and improving long-term survival rate^[24]. However,
10
11 283 the understanding of the effects of renal cancer radiotherapy has undergone a torturous process. In the
12
13 284 past sixty years, the radiotherapy community has conducted high-quality randomized controlled studies,
14
15 285 including preoperative radiotherapy, postoperative radiotherapy, and intraoperative radiotherapy for
16
17 286 renal cancer. Unfortunately, the conclusions of most studies show that radiotherapy does not improve
18
19 287 the efficacy, and in some cases, it reduces the efficacy as well^[25-27]. Coupled with the later
20
21 288 radiobiological studies suggesting that renal cancer is not sensitive to conventionally fractionated
22
23 289 radiotherapy^[28], the research on renal cancer radiotherapy has fallen into a trough. In fact, in historical
24
25 290 research, the backwardness of technology has led to insufficient doses. The prescribed doses given to
26
27 291 tumors do not meet the standards for radical treatment^[29]. At the same time, normal tissues are not well
28
29 292 protected, including the duodenum and liver, which have been exposed to excessive radiation.
30
31 293 SABR, also known as stereotactic body radiotherapy (SBRT), uses high-precision radiotherapy
32
33 294 technology to focus the radical radiation dose (single dose > 8-10 Gy) to the tumor site through external
34
35 295 irradiation to achieve the purpose of radical treatment of the tumor. It has the characteristics of high
36
37 296 precision, high dose, high conformability, and low treatment frequency. It has been gradually used in
38
39 297 the treatment of solid tumors such as liver cancer, lung cancer, and spinal tumors in recent years, with
40
41 298 definite curative effect^[30]. SABR was firstly clinically applied for stage I non-small cell lung carcinoma,
42
43 299 and related literature reports that the long-term local tumor control rate can reach 90%^[31].
44
45 300 In the existing researches on the treatment of renal cell carcinoma with SABR, the separated fractions
46
47 301 and radiation doses are different. A study^[16] found that the SABR regimen with 4 fractions and a total
48
49 302 radiation dose of 48 Gy has no significant dose-related adverse reactions, which is safe and feasible for
50
51 303 patients with localized renal cell carcinoma. Another study^[13] recommended using 5 fractions and a
52
53 304 total radiation dose of 35Gy to treat patients with inoperable metastatic renal cancer. The existing lead-in
54
55
56
57
58
59
60

1
2
3 305 trial results of SABR for RCC with IVCTT with a dose of 40Gy in 5 fractions has shown safety^[32].
4
5 306 Most SABR protocols often use 3 to 5 fractions^[33,34]. We choose tumor thrombus as the target organ of
6
7 307 radiotherapy, not including renal cancer tissue, to avoid the difficulty of surgical separation of the kidney
8
9 308 due to edema, fibrosis, or other reasons after irradiation. Since the growth level of the tumor thrombus
10
11 309 usually coincides with the horizontal part of the duodenum, the duodenal perforation will happen if the
12
13 310 radical dose of the tumor thrombus is taken. Based on the results of existing studies and to limit organ
14
15 311 toxicity, our trial design adopts a more conservative total radiation dose - 30Gy with 5 fractions.
16
17 312 Whether preoperative radiotherapy will increase the difficulty of the surgery is another important issue.
18
19 313 Existing research shows that preoperative radiotherapy for rectal cancer does not increase the difficulty
20
21 314 of operation and the incidence of postoperative complications^[35]. Based on this, we believe that a
22
23 315 reasonable neoadjuvant radiotherapy scheme will not increase the operation difficulty of renal cell
24
25 316 carcinoma and inferior vena cava tumor. Considering that the hyperemia and edema^[36,37] of tumor-
26
27 317 adjacent tissues in a short time after radiotherapy may increase the risk of surgery, we decide to operate
28
29 318 6-8 weeks after radiotherapy. At that time, the peritumoral edema will be reduced, and the tumor will
30
31 319 not continue to grow due to too long delay.
32
33 320 The clinical significances of this trial are as follows: ①For Mayo III-IV classification, it may reduce
34
35 321 the difficulty of operation, blood loss, blood transfusion rate, and perioperative complications. Some
36
37 322 cases of Mayo IV grade may require cardiac surgery interventions for complete surgical treatment^[38],
38
39 323 and preoperative radiotherapy may create the possibility of not needing cardiac surgery. ②For Mayo
40
41 324 II-IV classification, preoperative radiotherapy + surgery may be better than surgery alone, which
42
43 325 prolongs survival and reduces recurrence rate. ③When the tumor thrombus invades the inferior vena
44
45 326 cava wall in a wide range, preoperative radiotherapy can be used to preserve the inferior vena cava
46
47 327 vessel wall.
48
49 328 The pathological changes of tumors after radiotherapy have been proved to have prognostic significance
50
51 329 in other tumors^[22,39]. Tumors such as rectal cancer have clear grading standards, which are divided into
52
53 330 4 grades according to the degree of residual tumor after radiotherapy. Different grades correspond to
54
55
56
57
58
59
60

1
2
3 331 different prognoses. So far, this study is the only preoperative radiotherapy study in the world that
4
5 332 focuses on tumor thrombus, and is also a pioneering study on the prognostic value of pathological
6
7 333 changes after radiotherapy. Therefore, this study attempts to initially explore the post-radiotherapy
8
9 334 changes of renal tumor thrombus, and judge the prognosis of the tumor according to the different
10
11 335 pathological changes.

12
13 336 We hope to collect possible treatment data for a further large trial by this study.

14 15 16 337 **Trial Status**

17
18
19 338 Protocol version number: 2018-04-17. V2.30.

20
21 339 Recruitment began on 2018-05-01 and will be completed in 2021-12.

22 23 24 340 **Abbreviations**

25
26
27 341 AEs: adverse events; CRF: case report form; CTCAE: Common Terminology Criteria Adverse Events;
28
29 342 ECOG: Eastern Cooperative Oncology Group; GTV: gross tumor volume; IVCTT: inferior vena cava
30
31 343 tumor thrombus; OAR: organs at risk; PTV: planning target volume; RCC: Renal cell carcinoma; RFS:
32
33 344 Recurrent-free survival; SABR: stereotactic ablative body radiotherapy; SBRT: stereotactic body
34
35 345 radiotherapy

36 37 38 346 **Declarations**

39 40 41 42 347 **Patient and Public Involvement**

43
44
45 348 Patients or the public will not be involved in the design, or conduct, or reporting, or dissemination plans
46
47 349 of our research.

48 49 50 350 **Consent for publication**

51
52
53 351 Not applicable.

1
2
3 **352 Availability of data and materials**
4

5
6 **353** Researchers, monitors and reviewers of ethics committees will have access to the final trial dataset.
7

8
9 **354 Dissemination policy**
10

11 **355** Investigators and sponsor will communicate trial results to participants, healthcare professionals, the
12
13 **356** public, and other relevant groups via publication. The public will access to the full protocol, participant-
14
15 **357** level dataset, and statistical code from online database. Professional medical writers will complete an
16
17 **358** article of this trial.
18
19

20
21 **359 Authors' contributions**
22

23
24 **360** Project development: ZL, RP, JW, HW, LM; Wrote study protocol: YL, ZL, RP, RX; Wrote this
25
26 **361** manuscript: YL, ZL, RP; All authors have read and approved this manuscript, and ensure that this is the
27
28 **362** case.
29

30
31 **363 Funding statement**
32

33
34 **364** This work was supported by Peking University. The costs incurred in the research process are derived
35
36 **365** from the following funding: Project No. BMU2017YS001-2, which is detailed as the “Double First-
37
38 **366** Class” Advantage Discipline Construction Project of Peking University.
39
40

41
42 **367 Competing interests statement**
43

44
45 **368** The authors declare that they have no competing interests.
46
47

48 **369 Acknowledgements**
49

50
51 **370** The authors thank the entire staff of the Department of Urology and Department of Radiation Oncology,
52
53 **371** Peking University Third Hospital.
54
55

372 **References**

- 373 [1] Padala SA, Barsouk A, Thandra KC, et al. Epidemiology of Renal Cell Carcinoma[J]. *World*
374 *J Oncol*, 2020, 11(3): 79-87. doi: 10.14740/wjon1279
- 375 [2] Fusco V, Parisi S, d'Andrea B, et al. Role of radiotherapy in the treatment of renal cell
376 cancer: updated and critical review[J]. *Tumori*, 2017, 103(6): 504-510. doi:
377 10.5301/tj.5000640
- 378 [3] Blute ML, Leibovich BC, Lohse CM, et al. The Mayo Clinic experience with surgical
379 management, complications and outcome for patients with renal cell carcinoma and
380 venous tumour thrombus[J]. *BJU Int*, 2004, 94(1): 33-41. doi: 10.1111/j.1464-
381 410X.2004.04897.x
- 382 [4] Lawindy SM, Kurian T, Kim T, et al. Important surgical considerations in the management
383 of renal cell carcinoma (RCC) with inferior vena cava (IVC) tumour thrombus[J]. *BJU Int*,
384 2012, 110(7): 926-939. doi: 10.1111/j.1464-410X.2012.11174.x
- 385 [5] Ljungberg B, Cowan NC, Hanbury DC, et al. EAU guidelines on renal cell carcinoma: the
386 2010 update[J]. *Eur Urol*, 2010, 58(3): 398-406. doi: 10.1016/j.eururo.2010.06.032
- 387 [6] Hevia V, Ciancio G, Gómez V, et al. Surgical technique for the treatment of renal cell
388 carcinoma with inferior vena cava tumor thrombus: tips, tricks and oncological results[J].
389 *Springerplus*, 2016, 5: 132. doi: 10.1186/s40064-016-1825-1
- 390 [7] Ciancio G, Livingstone AS, Soloway M. Surgical management of renal cell carcinoma with
391 tumor thrombus in the renal and inferior vena cava: the University of Miami experience in
392 using liver transplantation techniques[J]. *Eur Urol*, 2007, 51(4): 988-994; discussion 994-
393 985. doi: 10.1016/j.eururo.2006.11.055
- 394 [8] Kakoti S, Jena R, Sureka SK, et al. Experience with management of renal cell carcinoma
395 with inferior vena cava/right atrial tumor thrombus[J]. *Indian J Urol*, 2021, 37(3): 234-240.
396 doi: 10.4103/iju.IJU_13_21
- 397 [9] Al Otaibi M, Abou Youssif T, Alkhalidi A, et al. Renal cell carcinoma with inferior vena caval
398 extention: impact of tumour extent on surgical outcome[J]. *BJU Int*, 2009, 104(10): 1467-
399 1470. doi: 10.1111/j.1464-410X.2009.08575.x
- 400 [10] Jibiki M, Iwai T, Inoue Y, et al. Surgical strategy for treating renal cell carcinoma with
401 thrombus extending into the inferior vena cava[J]. *J Vasc Surg*, 2004, 39(4): 829-835. doi:
402 10.1016/j.jvs.2003.12.004
- 403 [11] Siva S, Kothari G, Muacevic A, et al. Radiotherapy for renal cell carcinoma: renaissance
404 of an overlooked approach[J]. *Nat Rev Urol*, 2017, 14(9): 549-563. doi:
405 10.1038/nrurol.2017.87
- 406 [12] Singh AK, Winslow TB, Kermany MH, et al. A Pilot Study of Stereotactic Body Radiation
407 Therapy Combined with Cytoreductive Nephrectomy for Metastatic Renal Cell
408 Carcinoma[J]. *Clin Cancer Res*, 2017, 23(17): 5055-5065. doi: 10.1158/1078-0432.Ccr-16-
409 2946
- 410 [13] Correa RJM, Ahmad B, Warner A, et al. A prospective phase I dose-escalation trial of
411 stereotactic ablative radiotherapy (SABR) as an alternative to cytoreductive nephrectomy
412 for inoperable patients with metastatic renal cell carcinoma[J]. *Radiat Oncol*, 2018, 13(1):
413 47. doi: 10.1186/s13014-018-0992-3
- 414 [14] Teh B, Bloch C, Galli-Guevara M, et al. The treatment of primary and metastatic renal cell
415 carcinoma (RCC) with image-guided stereotactic body radiation therapy (SBRT)[J].
416 *Biomed Imaging Interv J*, 2007, 3(1): e6. doi: 10.2349/bij.3.1.e6
- 417 [15] Siva S, Jackson P, Kron T, et al. Impact of stereotactic radiotherapy on kidney function in

- 1
2
3 418 primary renal cell carcinoma: Establishing a dose-response relationship[J]. *Radiother*
4 419 *Oncol*, 2016, 118(3): 540-546. doi: 10.1016/j.radonc.2016.01.027
- 5 420 [16] Ponsky L, Lo SS, Zhang Y, et al. Phase I dose-escalation study of stereotactic body
6 421 radiotherapy (SBRT) for poor surgical candidates with localized renal cell carcinoma[J].
7 422 *Radiother Oncol*, 2015, 117(1): 183-187. doi: 10.1016/j.radonc.2015.08.030
- 8 423 [17] Svedman C, Sandström P, Pisa P, et al. A prospective Phase II trial of using extracranial
9 424 stereotactic radiotherapy in primary and metastatic renal cell carcinoma[J]. *Acta Oncol*,
10 425 2006, 45(7): 870-875. doi: 10.1080/02841860600954875
- 11 426 [18] Hannan R, Margulis V, Chun SG, et al. Stereotactic radiation therapy of renal cancer
12 427 inferior vena cava tumor thrombus[J]. *Cancer Biol Ther*, 2015, 16(5): 657-661. doi:
13 428 10.1080/15384047.2015.1026506
- 14 429 [19] Freifeld Y, Margulis V, Woldu SL, et al. Stereotactic Body Radiation Therapy for Renal Cell
15 430 Carcinoma with Inferior Vena Cava Thrombus – Initial Experience Report and Literature
16 431 Review[J]. *Kidney Cancer*, 2019, (3): 71-77. doi: 10.3233/KCA-180044
- 17 432 [20] <https://clinicaltrials.gov/ct2/show/study/NCT02473536>.
- 18 433 [21] Mandal S, Sankhwar SN, Kathpalia R, et al. Grading complications after transurethral
19 434 resection of prostate using modified Clavien classification system and predicting
20 435 complications using the Charlson comorbidity index[J]. *Int Urol Nephrol*, 2013, 45(2): 347-
21 436 354. doi: 10.1007/s11255-013-0399-x
- 22 437 [22] Lim SB, Hong SM, Yu CS, et al. Prevalence and clinical significance of acellular mucin in
23 438 locally advanced rectal cancer patients showing pathologic complete response to
24 439 preoperative chemoradiotherapy[J]. *Am J Surg Pathol*, 2013, 37(1): 47-52. doi:
25 440 10.1097/PAS.0b013e3182657186
- 26 441 [23] Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative
27 442 chemoradiotherapy for rectal cancer[J]. *N Engl J Med*, 2004, 351(17): 1731-1740. doi:
28 443 10.1056/NEJMoa040694
- 29 444 [24] Kapiteijn E, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with
30 445 total mesorectal excision for resectable rectal cancer[J]. *N Engl J Med*, 2001, 345(9): 638-
31 446 646. doi: 10.1056/NEJMoa010580
- 32 447 [25] Kjaer M, Iversen P, Hvidt V, et al. A randomized trial of postoperative radiotherapy versus
33 448 observation in stage II and III renal adenocarcinoma. A study by the Copenhagen Renal
34 449 Cancer Study Group[J]. *Scand J Urol Nephrol*, 1987, 21(4): 285-289. doi:
35 450 10.3109/00365598709180784
- 36 451 [26] Juusela H, Malmio K, Alfthan O, et al. Preoperative irradiation in the treatment of renal
37 452 adenocarcinoma[J]. *Scand J Urol Nephrol*, 1977, 11(3): 277-281. doi:
38 453 10.3109/00365597709179965
- 39 454 [27] Gez E, Libes M, Bar-Deroma R, et al. Postoperative irradiation in localized renal cell
40 455 carcinoma: the Rambam Medical Center experience[J]. *Tumori*, 2002, 88(6): 500-502. doi:
41 456 [28] Deschavanne PJ, Fertil B. A review of human cell radiosensitivity in vitro[J]. *Int J Radiat*
42 457 *Oncol Biol Phys*, 1996, 34(1): 251-266. doi: 10.1016/0360-3016(95)02029-2
- 43 458 [29] Dengina N, Tsimafeyeu I, Mitin T. Current Role of Radiotherapy for Renal-Cell Carcinoma:
44 459 Review[J]. *Clin Genitourin Cancer*, 2017, 15(2): 183-187. doi: 10.1016/j.clgc.2016.09.004
- 45 460 [30] Lo SS, Slotman BJ, Lock M, et al. The development of stereotactic body radiotherapy in
46 461 the past decade: a global perspective[J]. *Future Oncol*, 2015, 11(19): 2721-2733. doi:
47 462 10.2217/fon.15.220
- 48 463 [31] Kann BH, Miccio JA, Stahl JM, et al. Stereotactic body radiotherapy with adjuvant systemic
49 464 therapy for early-stage non-small cell lung carcinoma: A multi-institutional analysis[J].
50 465 *Radiother Oncol*, 2019, 132: 188-196. doi: 10.1016/j.radonc.2018.10.017

- 1
2
3 466 [32] Margulis V, Freifeld Y, Pop LM, et al. Neoadjuvant SABR for Renal Cell Carcinoma Inferior
4 467 Vena Cava Tumor Thrombus-Safety Lead-in Results of a Phase 2 Trial[J]. *Int J Radiat*
5 468 *Oncol Biol Phys*, 2021, 110(4): 1135-1142. doi: 10.1016/j.ijrobp.2021.01.054
6
7 469 [33] Siva S, Louie AV, Warner A, et al. Pooled analysis of stereotactic ablative radiotherapy for
8 470 primary renal cell carcinoma: A report from the International Radiosurgery Oncology
9 471 Consortium for Kidney (IROCK)[J]. *Cancer*, 2018, 124(5): 934-942. doi:
10 472 10.1002/cncr.31156
11 473 [34] Siva S, Ellis RJ, Ponsky L, et al. Consensus statement from the International Radiosurgery
12 474 Oncology Consortium for Kidney for primary renal cell carcinoma[J]. *Future Oncol*, 2016,
13 475 12(5): 637-645. doi: 10.2217/fon.16.2
14 476 [35] Valero G, Luján JA, Hernández Q, et al. Neoadjuvant radiation and chemotherapy in rectal
15 477 cancer does not increase postoperative complications[J]. *Int J Colorectal Dis*, 2003, 18(6):
16 478 495-499. doi: 10.1007/s00384-003-0520-1
17
18 479 [36] Li Y, Lin J, Xiao J, et al. Therapeutic effects of Co-Venenum Bufonis Oral Liquid on
19 480 radiation-induced esophagitis in rats[J]. *Exp Anim*, 2020, 69(3): 354-362. doi:
20 481 10.1538/expanim.19-0142
21 482 [37] Lee SR, Yang KA, Kim SK, et al. Radiation-induced intratumoral necrosis and peritumoral
22 483 edema after gamma knife radiosurgery for intracranial meningiomas[J]. *J Korean*
23 484 *Neurosurg Soc*, 2012, 52(2): 98-102. doi: 10.3340/jkns.2012.52.2.98
24
25 485 [38] Almohammad F, Bakour MM. Solitary fibrous renal tumor with thrombus extension into the
26 486 inferior vena cava and right atrium[J]. *Asian Cardiovasc Thorac Ann*, 2021, 29(8): 813-815.
27 487 doi: 10.1177/0218492321997391
28 488 [39] Chirieac LR, Swisher SG, Correa AM, et al. Signet-ring cell or mucinous histology after
29 489 preoperative chemoradiation and survival in patients with esophageal or esophagogastric
30 490 junction adenocarcinoma[J]. *Clin Cancer Res*, 2005, 11(6): 2229-2236. doi: 10.1158/1078-
31 491 0432.Ccr-04-1840
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 Figure 1. Flowchart for minimum assessments during treatment and follow up phase
4
5
6

7 Figure 2. Schematic outline of the treatment plan. Patients with renal cell carcinoma with Mayo II-IV
8 tumor thrombus will finish radiotherapy for thrombus area (total 30Gy). Radical nephrectomy and
9 thrombectomy will be performed between week 7~8. Follow up for secondary endpoints will be starting
10 at the date of nephrectomy and thrombectomy for 1 year every 3 months.
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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)

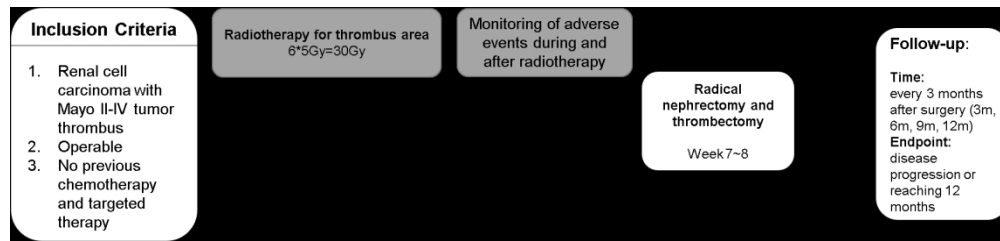


Figure 2. Schematic outline of the treatment plan. Patients with renal cell carcinoma with Mayo II-IV tumor thrombus will finish radiotherapy for thrombus area (total 30Gy). Radical nephrectomy and thrombectomy will be performed between week 7~8. Follow up for secondary endpoints will be starting at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

314x73mm (150 x 150 DPI)

1
2
3 Dear BMJ Open Editors:

4 On behalf of my co-authors, I am delighted to submit our protocol manuscript
5 entitled " Preoperative stereotactic body radiotherapy combined with surgical treatment
6 for renal cell carcinoma and inferior vena cava tumor thrombus: study protocol for a
7 single-arm cohort trial" to your appreciation and the editorial analysis of the BMJ Open,
8 as to the possibility of its publication.
9

10
11 In this manuscript, we developed a detailed study protocol aimed to evaluate the
12 safety of preoperative stereotactic radiotherapy combined with surgical treatment of
13 patients with renal cell carcinoma and inferior vena cava tumor thrombus (IVCTT). At
14 present, the traditional treatment used for RCC combined with IVCTT is radical
15 nephrectomy + IVC thrombectomy, which can improve patients' 5-year survival rate to
16 40%-60%. New methods are being urgently needed to further improve the survival rate
17 of patients. We believe that this manuscript is of great value to all researchers interested
18 in this particular complex disease.
19

20
21 Our Ethical Documentation was approved by the ethics committees of Peking
22 University Third Hospital. The trial is funded by Peking University. Our study protocol
23 has undergone peer-review by the funding body. Translated copies of the Ethical
24 Documentation and the Funding Approval Documentation have been uploaded.
25

26
27 Our study status is ongoing and has not completed participant recruitment at the
28 time of submission.

29
30 The manuscript has not been published before and is not being considered for
31 publication elsewhere. No publications containing the results of this study have already
32 been published or submitted to any journal. All authors have contributed to the creation
33 of this manuscript for important intellectual content and read and approved the final
34 manuscript, we declare there is no conflict of interest.
35

36
37 The number of words in this manuscript is 5724, which exceeds your limit,
38 because according to SPIRIT's regulations, data entry, protocol amendments, quality
39 control, stopping guidelines and other contents need to be added to this manuscript,
40 which will take up more words.

41 Your kind consideration will be greatly appreciated.

42 With best regards,

43 Yours sincerely,
44

45
46 Lulin Ma

47 Peking University Third Hospital

48 E-mail: malulinpku@163.com
49
50
51
52
53
54
55
56
57
58
59
60



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.

1			
2		11d	N/A. Not covered in our trial.
3			
4	Outcomes	12	Line 112-133
5			
6	Participant	13	Figure 1&2.
7	timeline		
8			
9	Sample size	14	Line 134-139
10			
11	Recruitment	15	Line 141-143
12			

Methods: Assignment of interventions (for controlled trials)

Allocation:

16	Sequence	16a	N/A. This is not a controlled trial.
17	generation		
18			
19			
20	Allocation	16b	N/A. This is not a controlled trial.
21	concealment		
22	mechanism		
23			
24	Implementation	16c	N/A. This is not a controlled trial.
25			
26	Blinding	17a	N/A. This is not a controlled trial.
27	(masking)		
28			
29		17b	N/A. This is not a controlled trial.
30			

Methods: Data collection, management, and analysis

33	Data collection	18a	Line 216-231
34	methods		
35			
36		18b	Line 232-233
37			
38	Data	19	Line 234-240
39	management		
40			
41			
42	Statistical	20a	Line 185-191
43	methods		
44			
45		20b	N/A. There are no additional analyses due to small sample size.
46			
47		20c	Line 192-193
48			

Methods: Monitoring

51	Data monitoring	21a	Line 245-264
52			
53		21b	Line 265-273
54			
55	Harms	22	Line 171-183
56			
57	Auditing	23	Line 246-249
58			

Ethics and dissemination

1			
2	Research ethics	24	Line 195-204
3	approval		
4			
5	Protocol	25	Line 241-244
6	amendments		
7			
8	Consent or assent	26a	Line 196-199
9			
10		26b	N/A. Participant data and biological specimens will not be used in
11			ancillary studies.
12			
13	Confidentiality	27	Line 205-211
14			
15	Declaration of	28	Line 368
16	interests		
17			
18	Access to data	29	Line 353
19			
20	Ancillary and	30	N/A. There is no compensation to those who suffer harm from trial
21	post-trial care		participation except medical care.
22			
23	Dissemination	31a	Line 355-358
24	policy		
25			
26		31b	Line 355-358
27			
28		31c	Line 355-358
29			
30			
31	Appendices		
32			
33	Informed consent	32	Line 196-199
34	materials		
35			
36	Biological	33	N/A. No biological specimens will be used for genetic or molecular
37	specimens		analysis.
38			

*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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" 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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-055364.R2
Article Type:	Protocol
Date Submitted by the Author:	06-Jan-2022
Complete List of Authors:	Liu, Yunchong; Peking University Third Hospital, Department of Urology Liu, Zhuo; Peking University Third Hospital, Department of Urology Peng, Ran; Peking University Third Hospital, Department of Radiation Oncology Xiao, Ruotao; Peking University Third Hospital, Department of Urology Wang, Junjie; Peking University Third Hospital, Department of Radiation Oncology Wang, Hao; Peking University Third Hospital, Department of Radiation Oncology Ma, Lulin; Peking University Third Hospital, Department of Urology
Primary Subject Heading:	Urology
Secondary Subject Heading:	Radiology and imaging
Keywords:	RADIOTHERAPY, Urological tumours < UROLOGY, Kidney tumours < ONCOLOGY

SCHOLARONE™
Manuscripts

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

1 Yunchong Liu^{1†}, Zhuo Liu^{1†}, Ran Peng^{2†}, Ruotao Xiao¹, Junjie Wang², Hao Wang^{2*} and
2 Lulin Ma^{1*}

3 ¹Department of Urology, Peking University Third Hospital, Beijing 100191, China.

4 ²Department of Radiation Oncology, Peking University Third Hospital, Beijing 100191, China.

5 [†]Yunchong Liu, Zhuo Liu, and Ran Peng contributed equally to this work.

6 *Correspondence: hhbysy@126.com; malulinpku@163.com

7 Abstract

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

13 **Methods and analysis:**

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

15 **Study treatment:** Preoperative stereotactic ablative radiotherapy combined with surgical treatment.

16 **Primary endpoints:** (1) Adverse reactions after 4-6 weeks of SABR. (2) Mayo staging of tumor
17 thrombus. (3) The length of the tumor thrombus from the corresponding anatomical mark. (4) Invasion

18 of the inferior vena cava wall. (5) Recurrent-free survival (RFS) rate of the tumor. (6) Cancer-specific
19 survival rate. (7) Overall survival rate. (8) Perioperative indicators including operation time,
20 intraoperative bleeding volume, and postoperative complications.

21 **Secondary endpoints:** (1) The longest diameter of the tumor. (2) Lymph node condition.

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

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

26 **Planned sample size:** 20 patients.

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

29 **Trial registration:** ChiCTR1800015118. Clinical trials on the safety and effectiveness of neoadjuvant
30 stereotactic radiotherapy combined with surgical treatment for patients with renal cell carcinoma with
31 inferior vena cava tumor thrombus. Registered 08 March 2018,
32 <http://www.chictr.org.cn/showproj.aspx?proj=25747>

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

35 **Strengths and limitations of this study**

36 Strengths

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

39 Limitations

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

42 Introduction

43 Renal cell carcinoma (RCC) is a common malignant tumor of the urinary system and accounts for 2~3%
44 of adult malignant tumors^[1]. Nearly 1/3 of the patients on presentation are locally advanced tumors
45 (2010 AJCC renal cancer stage III or IV) at the time of diagnosis^[2]. RCC has a tendency for venous
46 invasion and 4% to 10% of newly diagnosed cases have inferior vena cava tumor thrombus (IVCTT)^[3].
47 Currently, the traditional treatment used for RCC combined with IVCTT is surgery. Commonly used
48 surgical methods are open or laparoscopic radical nephrectomy + IVC thrombectomy^[4,5], which have a
49 high risk and require extremely proficient operating skills and surgical capabilities of the doctor^[6-8].
50 Open or laparoscopic surgery may have early postoperative complications, such as bleeding, lung
51 infection, deep vein thrombosis of the lower limbs, pulmonary embolism, renal failure, liver failure,
52 urinary fistula, chylous fistula, and so on. Severe complications can even lead to death^[3].
53 At present, the main problems in the treatment of RCC combined with IVCTT can be summarized in
54 the following aspects: ① The operation is with high difficulties, risks, and many complications^[3]. ②
55 For Mayo I -IV grade, radical nephrectomy + IVC thrombectomy can improve the 5-year survival rate
56 of patients, but it can only reach 40%-60%^[9]. How to further improve the survival rate of patients is a
57 hot research topic. ③ When the tumor thrombus invades the inferior vena cava wall in a wide range,
58 segmental resection of the inferior vena cava is required^[10]. Lower limb edema and renal insufficiency
59 may occur after surgery.
60 Nowadays, the equipment, technology, and concept of radiotherapy have ushered in a leap-forward
61 development. The development of intensity-modulated radiotherapy technology has allowed tumors and
62 surrounding normal tissues to obtain completely different doses. Image-guided technology allows the
63 doses given from the radiotherapy plan to hit the tumor accurately. Stereotactic ablative body
64 radiotherapy (SABR) has greatly expanded and partially subverted the understanding of traditional
65 radiobiology^[11]. In the past 10 years, new explorations of renal cancer have been continuously reported,
66 mainly confined to inoperable renal cancer patients, all using SABR technology, and its local control

67 rate and survival rate have reached a high level^[12-17]. Many phase-II SABR clinical trials for renal cell
68 carcinoma are ongoing (NCT02141919, NCT01890590, NCT02613819, NCT03747133, and
69 NCT03108703). Combined with the good results achieved by the SABR technique in inoperable renal
70 cancer patients, we expect that it can shrink and reduce the level of tumor thrombus, increase surgical
71 resection rate, and reduce surgical risk. Evidence has shown that SABR can reduce the transverse
72 diameter of the tumor thrombus^[18], which may help solve the problem of venous obstruction by tumor
73 thrombus. And the team's long-term follow-up results of two cases showed that SABR to RCC with
74 IVCTT could get good local tumor control in selected patients^[19]. Its safety and effectiveness need to
75 be further examined.

76 **Aims**

77 To determine the safety of the treatment by the study of preoperative stereotactic radiotherapy combined
78 with surgical treatment of patients with renal cell carcinoma and inferior vena cava tumor thrombus.
79 Main purpose: 1. To identify the acute and late toxicity of radiotherapy. Severe toxicity is defined as
80 grade III-IV toxicity according to Common Terminology Criteria Adverse Events (CTCAE) v4.0. 2.
81 Secondary purpose: To identify whether the difficulty or risk of surgery is increased after radiotherapy
82 by analyzing perioperative complications, operation time, intraoperative bleeding volume,
83 intraoperative transfusion volume of suspended red blood cells, and postoperative hospital stay. Using
84 the follow-up data of the patients to clarify the curative effect of the treatment: 1. For Mayo III-IV
85 classification, it may reduce the difficulty of operation, blood loss, blood transfusion rate and
86 perioperative complications. 2. For Mayo II-IV classification, preoperative radiotherapy + surgery may
87 be better than surgery alone, which prolongs survival and reduces recurrence rate. 3. When the tumor
88 thrombus invades the inferior vena cava wall in a wide range, preoperative radiotherapy can be used to
89 preserve the inferior vena cava vessel wall.

90 **Methods and Analysis**

91 **Study design**

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

93 **Inclusion criteria**

94 (1) Age \geq 18 years old.

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

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

97 (4) Subjects eligible for SABR for IVC tumor thrombosis at the decision of the radiation oncologist.

98 (5) Subjects eligible for radical nephrectomy and inferior vena cava thrombectomy at the decision
99 of urologists.

100 (6) ECOG 0-2.

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

102 **Exclusion criteria**

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

105 (2) Subjects with a history of preoperative targeted therapy, preoperative chemotherapy, or other
106 related treatments.

107 (3) Subjects with a history of pulmonary embolism.

108 (4) Subjects with severe cardiopulmonary insufficiency, severe arrhythmia, myocardial infarction,
109 angina pectoris, severe coagulation disease, or severe liver disease that cannot tolerate SABR or surgery.

110 (5) Subjects with diseases that severely affect the judgment of patients, such as mental disorders.

1
2
3 111 **Endpoints**
4
5

6 112 *Primary endpoints*
7

8
9 113 (1) Adverse reactions after 4-6 weeks of SABR. Measurement time point: 4-6 weeks after SABR
10 114 treatment. Measurement method: observation and inspection.

11 115 (2) Mayo staging of tumor thrombus. Measurement time point: before and after radiotherapy.
12 116 Measurement method: CT or MRI.

13 117 (3) The length of the tumor thrombus from the corresponding anatomical mark. Measurement time
14 118 point: before and after radiotherapy. Measurement method: CT or MRI.

15 119 (4) Invasion of the inferior vena cava wall. Measurement time point: before and after radiotherapy.
16 120 Measurement method: CT or MRI.

17 121 (5) Recurrent-free survival (RFS) rate of the tumor. Measurement time point: postoperative.
18 122 Measurement method: CT or MRI, follow-up.

19 123 (6) Cancer-specific survival rate. Measurement time point: postoperative. Measurement method:
20 124 follow-up.

21 125 (7) Overall survival rate. Measurement time point: postoperative. Measurement method: follow-up.

22 126 (8) Perioperative indicators including operation time, intraoperative bleeding volume, and
23 127 postoperative complications. Measurement time point: postoperative. Measurement method: surgical
24 128 record or observation and inspection.

25
26
27
28
29
30
31
32
33 129 *Secondary endpoints*
34

35 130 (1) The longest diameter of the tumor. Measurement time point: before and after radiotherapy.
36 131 Measurement method: CT or MRI.

37 132 (2) Lymph node condition. Measurement time point: before and after radiotherapy. Measurement
38 133 method: CT or MRI.
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 **134 Statistical calculations for trial sample size**
4
5

6 **135** This study is based on the registered clinical trial study "Neo-adjuvant SABR for IVC Tumor Thrombus
7
8 **136** in Newly Diagnosed RCC"^[20] retrieved on the Clinical trial website. It's a single-arm study and the
9
10 **137** sample size is 6 for lead-in phase and 23 for phase II. In our study, there is only one intervention group.
11
12 **138** The study will be conducted after the intervention. The focus is on the safety of the trial. The sample
13
14 **139** size is estimated to be 20 cases.
15

16
17 **140 Treatment and follow up**
18

19
20 **141** 20 patients enrolled from outpatient service of Peking University Third Hospital in the intervention
21
22 **142** group are treated with preoperative SABR to assist surgery. A total radiation dose of 30 Gy with 5
23
24 **143** fractions will be given to IVC of each patient.
25

26 **144** Simulation before radiotherapy will start on day 1. The subject lies on his back with hands at his sides.
27
28 **145** The fixation technology of the negative pressure vacuum bag is utilized to fix his head, body, and limbs
29
30 **146** simultaneously with a foot pedal. Using CT, MRI, and PET-CT to scan the upper boundary of the tumor
31
32 **147** $\geq 15\text{cm}$ upward, and the lower boundary $\geq 15\text{cm}$ as the scanning range. CT images include unenhanced
33
34 **148** phase (as the reference image), arterial phase, and venous phase with a slice thickness of 1-1.5mm. MRI
35
36 **149** images include T1WI, T2WI, enhanced and DWI phases with a slice thickness of 1-3mm. Target
37
38 **150** delineation will start on day 2. CT, MRI, and PET-CT fusion will be performed, with CT unenhanced
39
40 **151** phase as the reference image to delineate the target area. Delineating vena cava tumor thrombus as gross
41
42 **152** tumor volume (GTV) and stomach, duodenum, jejunum, ileum, colon, spinal cord, liver, esophagus as
43
44 **153** organs at risk (OAR). The planning target volume (PTV) is generated by adding a 3mm margin around
45
46 **154** the GTV. On day 3, a prescription dose of PTV 30Gy/5Gy/6f over 1 week is designed by a senior
47
48 **155** medical physicist and approved by an expert. This prescription then will be uploaded to Accuray
49
50 **156** MultiPlan® (Accuray Inc., Sunnyvale, CA) treatment planning system. On day 4, cyberknife
51
52 **157** (CyberKnife® VSI™, Accuray Inc., Sunnyvale, CA) radiotherapy will be carried out following the
53
54 **158** radiotherapy plan after the treatment list signed and confirmed by the radiotherapist in charge and the
55
56
57
58
59
60

1
2
3 159 planning physicist. Two or more therapists will perform the radiotherapy. During the first treatment, the
4
5 160 radiotherapist and physicist will jointly participate in the location verification.
6

7 161 After 4-6 weeks of rest, re-admission to finish blood routine, blood biochemistry, coagulation function,
8
9 162 urine routine, enhanced CT of the urinary system, enhanced MRI of inferior vena cava on re-admission
10
11 163 day 1. Complete pre-operation preparations on re-admission day 3. Radical nephrectomy + IVC
12
13 164 thrombectomy will be performed on re-admission day 4.
14

15 165 Post-surgery visits at 1, 2, 3, 7 days and the day leaving hospital and 3, 6, 9, 12 months after the date of
16
17 166 radical nephrectomy and IVC thrombectomy include blood routine, blood biochemistry, erythrocyte
18
19 167 sedimentation rate, coagulation function, and urine routine.
20

21 168 Subjects will receive regular phone calls from the investigators to complete follow-up.
22

23 169 A SPIRIT figure of detailed flowchart for minimum assessments during the treatment and follow-up
24
25 170 phase is shown in Figure 1. A schematic outline of the treatment plan is shown in Figure 2.
26

27 28 171 **Adverse events**

29
30
31 172 Adverse events (AEs) for radiation and surgery will be collected respectively.
32

33 173 SABR-related AEs are defined using Common Terminology Criteria for Adverse Events (CTCAE) v4.0.
34

35 174 We are interested in acute and late toxicity including nausea, fatigue, anorexia, diarrhea, enteritis,
36
37 175 gastritis, fistula, dermatitis, anemia, lymphopenia, neutropenia, thrombocytopenia, and ALT/AST
38
39 176 elevation. Severe toxicity is defined as grade III-IV toxicity according to CTCAE v4.0.
40

41 177 Modified Clavien classification system^[21] is used to evaluate adverse events in terms of surgery.
42

43 178 Surgical AEs of interest are postoperative active bleeding, postoperative anemia, wound infection,
44
45 179 pulmonary infection, lower extremity deep vein thrombosis, pulmonary embolism, chylous fistula, renal
46
47 180 dysfunction, hyperkalemia, and continuous venovenous hemodiafiltration.
48

49 181 If any serious adverse event or important adverse event occurs, regardless of whether it is related to the
50
51 182 research intervention, or whether the intervention has been implemented, the investigator must be
52
53 183 notified by telephone/fax within 24 hours of the occurrence.
54
55
56
57
58
59
60

184 **Data analysis**

185 The enumeration data are described by case number and percentage, and chi square test is used. Rank
186 sum test is used to compare the rank data. The measurement data are expressed by means + standard
187 deviation. If the measurement data conform to normal distribution, independent sample t-test or analysis
188 of variance is used. The Kaplan-Meier method will be used to calculate the tumor-free rate, tumor-
189 specific survival rate, and overall survival rate with SPSS 18.0 software, and the Log-rank test will be
190 performed. The comparability of data and the comparison of short-term efficacy before and after the
191 test will be tested by Fisher's exact probability method. $P < 0.05$ is considered statistically significant.
192 Intention-to-treat analysis is used for the results of subjects who drop out, lost to follow-up or do not
193 complete the trial process. Multiple imputation is used for missing data.

194 **Ethics and dissemination**

195 **Ethics, informed consent and safety**

196 The trial protocol and the informed consent of the subjects were submitted and approved by the Peking
197 University Biomedical Ethics Committee. The written informed consent form will be obtained from all
198 individual participants in the study. The specific contents of the informed consent form are provided in
199 the supplementary materials. If the protocol is revised, only the corresponding revised part and the
200 revised informed consent form (if any) can be implemented after being reviewed and approved by the
201 ethics committee, and a copy of the approval of the Peking University Biomedical Ethics Committee is
202 required to be provided to the clinical monitor. If the revision of the protocol aims to reduce the clear
203 risk of the subjects, it can be implemented immediately, but it must be submitted to the relevant
204 departments and the ethics committee for a record as soon as possible.

205 **Confidentiality**

206 The data involved in the research process will be taken care of to protect the privacy of the subjects. For

207 example, the identification code table contains information such as the subject's name, phone number,
208 ID number, and home address. Researchers will keep it properly and take it out for inquiry when follow-
209 up is needed. In addition, the cover and information page of case report form (CRF) will record the
210 subject's initials rather than the signature of the name, and the informed consent signed by the subject
211 will be kept separately from other information to prevent the disclosure of the subject's information.

212 **Trial organization**

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

216 **Data entry**

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

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

224 **Contents and methods of data verification and management**

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

229 At the review meeting, the main researchers, monitors, data administrators, and statisticians make
230 decisions on the subjects' informed consent and issues raised in the database inspection report, and write

1
2
3 231 a review report. The database will be locked at the same time.

4
5 232 To promote participant retention and complete follow-up, researchers should do a good job of subject

6
7 233 compliance education during the process of informed consent and follow-up.

8
9
10 234 **Data storage**

11
12
13 235 After completing the data entry and verification as required, the case report form will be archived and

14
15 236 stored in the order of numbers, and filled with a search catalog for future reference. Electronic data files

16
17 237 include databases, inspection procedures, analysis procedures, analysis results, codebooks, and

18
19 238 description files, etc., which will be stored in categories, and multiple backups will be stored on different

20
21 239 disks or recording media, and they will be stored properly to prevent damage. All original archives will

22
23 240 be kept within the corresponding period.

24
25
26 241 **Protocol amendments**

27
28
29 242 When the supervisors find that the phenomenon of non-compliance with the inclusion criteria persists,

30
31 243 or the selection criteria are too strict, resulting in a low number of subjects, a supervision meeting will

32
33 244 be carried out to amend the protocol.

34
35
36 245 **Quality Control**

37
38
39 246 During the trial and research process, clinical monitors will be assigned to conduct regular on-site

40
41 247 supervision visits to the research to ensure that all the contents of the research plan are strictly followed

42
43 248 and the information filled in is correct. the process will be independent from investigators and the

44
45 249 sponsor. The test center shall objectively and truthfully record and retain all data and the execution and

46
47 250 modification of the program during the test and research process. During the recruitment phase, the

48
49 251 consistency of the selection/exclusion criteria will be ensured as much as possible.

50
51 252 The specific supervision contents are as follows:

52
53 253 (1) The research plan is submitted to the ethics committee for approval.

54
55 254 (2) Participants in this study carefully implement the standard operating procedures for clinical

1
2
3 255 verification before, during and after verification.
4

5 256 (3) During the research process, the inspectors from the clinical trial research unit and the implementer
6
7 257 monitor the correctness and completeness of the data in the CRF.
8

9 258 (4) Researchers must undergo unified training, unified recording methods and judgment standards.
10

11 259 (5) The investigator will fill in the case report form according to the requirements, truthfully, in detail,
12
13 260 and carefully record the contents of the CRF to ensure that the content of the case report form is true
14
15 261 and reliable.
16

17 262 (6) All observations and findings in clinical research will be verified to ensure that the conclusions in
18
19 263 the clinical verification are derived from the original data, and there are corresponding data management
20
21 264 measures in the clinical verification and data processing.
22

23 24 265 **Stopping guidelines**

25
26
27 266 The principles and treatment methods for early termination of the study, including:

28
29 267 (1) If serious safety problems are found in the trial, the clinical trial will be terminated in time.

30
31 268 (2) The treatment effect of the experimental program is too poor, or even ineffective, and has no clinical
32
33 269 value.
34

35 270 (3) There are major mistakes in the clinical trial protocol or serious deviations in the implementation,
36
37 271 and it is difficult to evaluate the therapeutic effect.
38

39 272 (4) The applicant requests to terminate the experiment or the administrative department requests to
40
41 273 terminate the experiment.
42

43 44 45 274 **Discussion**

46
47
48
49 275 This study aims to evaluate the safety of the treatment by the study of preoperative stereotactic
50
51 276 radiotherapy combined with surgical treatment of patients with renal cell carcinoma and inferior vena
52
53 277 cava tumor thrombus.

54
55 278 Preoperative radiotherapy has been proven effective in many tumors, including rectal cancer,
56

1
2
3 279 esophageal cancer, and soft tissue sarcoma. Taking rectal cancer as an example, compared with surgery
4
5 280 alone, the effects of preoperative radiotherapy are mainly reflected in ①Reducing clinical staging and
6
7 281 increasing surgical resection rate^[22]. ②Increasing anus preservation rate and improving patients'
8
9 282 quality of life^[23]. ③Reducing local recurrence rate and improving long-term survival rate^[24]. However,
10
11 283 the understanding of the effects of renal cancer radiotherapy has undergone a torturous process. In the
12
13 284 past sixty years, the radiotherapy community has conducted high-quality randomized controlled studies,
14
15 285 including preoperative radiotherapy, postoperative radiotherapy, and intraoperative radiotherapy for
16
17 286 renal cancer. Unfortunately, the conclusions of most studies show that radiotherapy does not improve
18
19 287 the efficacy, and in some cases, it reduces the efficacy as well^[25-27]. Coupled with the later
20
21 288 radiobiological studies suggesting that renal cancer is not sensitive to conventionally fractionated
22
23 289 radiotherapy^[28], the research on renal cancer radiotherapy has fallen into a trough. In fact, in historical
24
25 290 research, the backwardness of technology has led to insufficient doses. The prescribed doses given to
26
27 291 tumors do not meet the standards for radical treatment^[29]. At the same time, normal tissues are not well
28
29 292 protected, including the duodenum and liver, which have been exposed to excessive radiation.
30
31 293 SABR, also known as stereotactic body radiotherapy (SBRT), uses high-precision radiotherapy
32
33 294 technology to focus the radical radiation dose (single dose > 8-10 Gy) to the tumor site through external
34
35 295 irradiation to achieve the purpose of radical treatment of the tumor. It has the characteristics of high
36
37 296 precision, high dose, high conformability, and low treatment frequency. It has been gradually used in
38
39 297 the treatment of solid tumors such as liver cancer, lung cancer, and spinal tumors in recent years, with
40
41 298 definite curative effect^[30]. SABR was firstly clinically applied for stage I non-small cell lung carcinoma,
42
43 299 and related literature reports that the long-term local tumor control rate can reach 90%^[31].
44
45 300 In the existing researches on the treatment of renal cell carcinoma with SABR, the separated fractions
46
47 301 and radiation doses are different. A study^[16] found that the SABR regimen with 4 fractions and a total
48
49 302 radiation dose of 48 Gy has no significant dose-related adverse reactions, which is safe and feasible for
50
51 303 patients with localized renal cell carcinoma. Another study^[13] recommended using 5 fractions and a
52
53 304 total radiation dose of 35Gy to treat patients with inoperable metastatic renal cancer. The existing lead-in
54
55
56
57
58
59
60

1
2
3 305 trial results of SABR for RCC with IVCTT with a dose of 40Gy in 5 fractions has shown safety^[32].
4
5 306 Most SABR protocols often use 3 to 5 fractions^[33,34]. We choose tumor thrombus as the target organ of
6
7 307 radiotherapy, not including renal cancer tissue, to avoid the difficulty of surgical separation of the kidney
8
9 308 due to edema, fibrosis, or other reasons after irradiation. Since the growth level of the tumor thrombus
10
11 309 usually coincides with the horizontal part of the duodenum, the duodenal perforation will happen if the
12
13 310 radical dose of the tumor thrombus is taken. Based on the results of existing studies and to limit organ
14
15 311 toxicity, our trial design adopts a more conservative total radiation dose - 30Gy with 5 fractions.
16
17 312 Whether preoperative radiotherapy will increase the difficulty of the surgery is another important issue.
18
19 313 Existing research shows that preoperative radiotherapy for rectal cancer does not increase the difficulty
20
21 314 of operation and the incidence of postoperative complications^[35]. Based on this, we believe that a
22
23 315 reasonable neoadjuvant radiotherapy scheme will not increase the operation difficulty of renal cell
24
25 316 carcinoma and inferior vena cava tumor. Considering that the hyperemia and edema^[36,37] of tumor-
26
27 317 adjacent tissues in a short time after radiotherapy may increase the risk of surgery, we decide to operate
28
29 318 6-8 weeks after radiotherapy. At that time, the peritumoral edema will be reduced, and the tumor will
30
31 319 not continue to grow due to too long delay.
32
33 320 The clinical significances of this trial are as follows: ①For Mayo III-IV classification, it may reduce
34
35 321 the difficulty of operation, blood loss, blood transfusion rate, and perioperative complications. Some
36
37 322 cases of Mayo IV grade may require cardiac surgery interventions for complete surgical treatment^[38],
38
39 323 and preoperative radiotherapy may create the possibility of not needing cardiac surgery. ②For Mayo
40
41 324 II-IV classification, preoperative radiotherapy + surgery may be better than surgery alone, which
42
43 325 prolongs survival and reduces recurrence rate. ③When the tumor thrombus invades the inferior vena
44
45 326 cava wall in a wide range, preoperative radiotherapy can be used to preserve the inferior vena cava
46
47 327 vessel wall.
48
49 328 The pathological changes of tumors after radiotherapy have been proved to have prognostic significance
50
51 329 in other tumors^[22,39]. Tumors such as rectal cancer have clear grading standards, which are divided into
52
53 330 4 grades according to the degree of residual tumor after radiotherapy. Different grades correspond to
54
55
56
57
58
59
60

1
2
3 331 different prognoses. So far, this study is the only preoperative radiotherapy study in the world that
4
5 332 focuses on tumor thrombus, and is also a pioneering study on the prognostic value of pathological
6
7 333 changes after radiotherapy. Therefore, this study attempts to initially explore the post-radiotherapy
8
9 334 changes of renal tumor thrombus, and judge the prognosis of the tumor according to the different
10
11 335 pathological changes.

12
13 336 We hope to collect possible treatment data for a further large trial by this study.

14 15 16 337 **Trial Status**

17
18
19 338 Protocol version number: 2018-04-17. V2.30.

20
21 339 Recruitment began on 2018-05-01 and will be completed in 2021-12.

22 23 24 340 **Abbreviations**

25
26
27 341 AEs: adverse events; CRF: case report form; CTCAE: Common Terminology Criteria Adverse Events;
28
29 342 ECOG: Eastern Cooperative Oncology Group; GTV: gross tumor volume; IVCTT: inferior vena cava
30
31 343 tumor thrombus; OAR: organs at risk; PTV: planning target volume; RCC: Renal cell carcinoma; RFS:
32
33 344 Recurrent-free survival; SABR: stereotactic ablative body radiotherapy; SBRT: stereotactic body
34
35 345 radiotherapy

36 37 38 346 **Declarations**

39 40 41 42 347 **Patient and Public Involvement**

43
44
45 348 Patients or the public will not be involved in the design, or conduct, or reporting, or dissemination plans
46
47 349 of our research.

48 49 50 350 **Consent for publication**

51
52
53 351 Not applicable.

1
2
3 **352 Availability of data and materials**
4

5
6 **353** Researchers, monitors and reviewers of ethics committees will have access to the final trial dataset.
7

8
9 **354 Dissemination policy**
10

11 **355** Investigators and sponsor will communicate trial results to participants, healthcare professionals, the
12 public, and other relevant groups via publication. The public will access to the full protocol, participant-
13 **356** level dataset, and statistical code from online database. Professional medical writers will complete an
14 **357** article of this trial.
15
16
17
18
19

20
21 **359 Authors' contributions**
22

23
24 **360** Project development: ZL, RP, JW, HW, LM; Wrote study protocol: YL, ZL, RP, RX; Wrote this
25 manuscript: YL, ZL, RP; All authors have read and approved this manuscript, and ensure that this is the
26 **361** case.
27
28
29

30
31 **363 Funding statement**
32

33
34 **364** This work was supported by Peking University. The costs incurred in the research process are derived
35 from the following funding: Project No. BMU2017YS001-2, which is detailed as the “Double First-
36 **365** Class” Advantage Discipline Construction Project of Peking University.
37
38
39

40
41 **367 Competing interests statement**
42

43
44 **368** The authors declare that they have no competing interests.
45

46
47 **369 Acknowledgements**
48

49
50 **370** The authors thank the entire staff of the Department of Urology and Department of Radiation Oncology,
51 Peking University Third Hospital.
52
53
54
55

372 **References**

- 373 [1] Padala SA, Barsouk A, Thandra KC, et al. Epidemiology of Renal Cell Carcinoma[J]. *World*
374 *J Oncol*, 2020, 11(3): 79-87. doi: 10.14740/wjon1279
- 375 [2] Fusco V, Parisi S, d'Andrea B, et al. Role of radiotherapy in the treatment of renal cell
376 cancer: updated and critical review[J]. *Tumori*, 2017, 103(6): 504-510. doi:
377 10.5301/tj.5000640
- 378 [3] Blute ML, Leibovich BC, Lohse CM, et al. The Mayo Clinic experience with surgical
379 management, complications and outcome for patients with renal cell carcinoma and
380 venous tumour thrombus[J]. *BJU Int*, 2004, 94(1): 33-41. doi: 10.1111/j.1464-
381 410X.2004.04897.x
- 382 [4] Lawindy SM, Kurian T, Kim T, et al. Important surgical considerations in the management
383 of renal cell carcinoma (RCC) with inferior vena cava (IVC) tumour thrombus[J]. *BJU Int*,
384 2012, 110(7): 926-939. doi: 10.1111/j.1464-410X.2012.11174.x
- 385 [5] Ljungberg B, Cowan NC, Hanbury DC, et al. EAU guidelines on renal cell carcinoma: the
386 2010 update[J]. *Eur Urol*, 2010, 58(3): 398-406. doi: 10.1016/j.eururo.2010.06.032
- 387 [6] Hevia V, Ciancio G, Gómez V, et al. Surgical technique for the treatment of renal cell
388 carcinoma with inferior vena cava tumor thrombus: tips, tricks and oncological results[J].
389 *Springerplus*, 2016, 5: 132. doi: 10.1186/s40064-016-1825-1
- 390 [7] Ciancio G, Livingstone AS, Soloway M. Surgical management of renal cell carcinoma with
391 tumor thrombus in the renal and inferior vena cava: the University of Miami experience in
392 using liver transplantation techniques[J]. *Eur Urol*, 2007, 51(4): 988-994; discussion 994-
393 985. doi: 10.1016/j.eururo.2006.11.055
- 394 [8] Kakoti S, Jena R, Sureka SK, et al. Experience with management of renal cell carcinoma
395 with inferior vena cava/right atrial tumor thrombus[J]. *Indian J Urol*, 2021, 37(3): 234-240.
396 doi: 10.4103/iju.IJU_13_21
- 397 [9] Al Otaibi M, Abou Youssif T, Alkhalidi A, et al. Renal cell carcinoma with inferior vena caval
398 extention: impact of tumour extent on surgical outcome[J]. *BJU Int*, 2009, 104(10): 1467-
399 1470. doi: 10.1111/j.1464-410X.2009.08575.x
- 400 [10] Jibiki M, Iwai T, Inoue Y, et al. Surgical strategy for treating renal cell carcinoma with
401 thrombus extending into the inferior vena cava[J]. *J Vasc Surg*, 2004, 39(4): 829-835. doi:
402 10.1016/j.jvs.2003.12.004
- 403 [11] Siva S, Kothari G, Muacevic A, et al. Radiotherapy for renal cell carcinoma: renaissance
404 of an overlooked approach[J]. *Nat Rev Urol*, 2017, 14(9): 549-563. doi:
405 10.1038/nrurol.2017.87
- 406 [12] Singh AK, Winslow TB, Kermany MH, et al. A Pilot Study of Stereotactic Body Radiation
407 Therapy Combined with Cytoreductive Nephrectomy for Metastatic Renal Cell
408 Carcinoma[J]. *Clin Cancer Res*, 2017, 23(17): 5055-5065. doi: 10.1158/1078-0432.Ccr-16-
409 2946
- 410 [13] Correa RJM, Ahmad B, Warner A, et al. A prospective phase I dose-escalation trial of
411 stereotactic ablative radiotherapy (SABR) as an alternative to cytoreductive nephrectomy
412 for inoperable patients with metastatic renal cell carcinoma[J]. *Radiat Oncol*, 2018, 13(1):
413 47. doi: 10.1186/s13014-018-0992-3
- 414 [14] Teh B, Bloch C, Galli-Guevara M, et al. The treatment of primary and metastatic renal cell
415 carcinoma (RCC) with image-guided stereotactic body radiation therapy (SBRT)[J].
416 *Biomed Imaging Interv J*, 2007, 3(1): e6. doi: 10.2349/bij.3.1.e6
- 417 [15] Siva S, Jackson P, Kron T, et al. Impact of stereotactic radiotherapy on kidney function in

- 1
2
3 418 primary renal cell carcinoma: Establishing a dose-response relationship[J]. *Radiother*
4 419 *Oncol*, 2016, 118(3): 540-546. doi: 10.1016/j.radonc.2016.01.027
- 5 420 [16] Ponsky L, Lo SS, Zhang Y, et al. Phase I dose-escalation study of stereotactic body
6 421 radiotherapy (SBRT) for poor surgical candidates with localized renal cell carcinoma[J].
7 422 *Radiother Oncol*, 2015, 117(1): 183-187. doi: 10.1016/j.radonc.2015.08.030
- 8 423 [17] Svedman C, Sandström P, Pisa P, et al. A prospective Phase II trial of using extracranial
9 424 stereotactic radiotherapy in primary and metastatic renal cell carcinoma[J]. *Acta Oncol*,
10 425 2006, 45(7): 870-875. doi: 10.1080/02841860600954875
- 11 426 [18] Hannan R, Margulis V, Chun SG, et al. Stereotactic radiation therapy of renal cancer
12 427 inferior vena cava tumor thrombus[J]. *Cancer Biol Ther*, 2015, 16(5): 657-661. doi:
13 428 10.1080/15384047.2015.1026506
- 14 429 [19] Freifeld Y, Margulis V, Woldu SL, et al. Stereotactic Body Radiation Therapy for Renal Cell
15 430 Carcinoma with Inferior Vena Cava Thrombus – Initial Experience Report and Literature
16 431 Review[J]. *Kidney Cancer*, 2019, (3): 71-77. doi: 10.3233/KCA-180044
- 17 432 [20] <https://clinicaltrials.gov/ct2/show/study/NCT02473536>.
- 18 433 [21] Mandal S, Sankhwar SN, Kathpalia R, et al. Grading complications after transurethral
19 434 resection of prostate using modified Clavien classification system and predicting
20 435 complications using the Charlson comorbidity index[J]. *Int Urol Nephrol*, 2013, 45(2): 347-
21 436 354. doi: 10.1007/s11255-013-0399-x
- 22 437 [22] Lim SB, Hong SM, Yu CS, et al. Prevalence and clinical significance of acellular mucin in
23 438 locally advanced rectal cancer patients showing pathologic complete response to
24 439 preoperative chemoradiotherapy[J]. *Am J Surg Pathol*, 2013, 37(1): 47-52. doi:
25 440 10.1097/PAS.0b013e3182657186
- 26 441 [23] Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative
27 442 chemoradiotherapy for rectal cancer[J]. *N Engl J Med*, 2004, 351(17): 1731-1740. doi:
28 443 10.1056/NEJMoa040694
- 29 444 [24] Kapiteijn E, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with
30 445 total mesorectal excision for resectable rectal cancer[J]. *N Engl J Med*, 2001, 345(9): 638-
31 446 646. doi: 10.1056/NEJMoa010580
- 32 447 [25] Kjaer M, Iversen P, Hvidt V, et al. A randomized trial of postoperative radiotherapy versus
33 448 observation in stage II and III renal adenocarcinoma. A study by the Copenhagen Renal
34 449 Cancer Study Group[J]. *Scand J Urol Nephrol*, 1987, 21(4): 285-289. doi:
35 450 10.3109/00365598709180784
- 36 451 [26] Juusela H, Malmio K, Alfthan O, et al. Preoperative irradiation in the treatment of renal
37 452 adenocarcinoma[J]. *Scand J Urol Nephrol*, 1977, 11(3): 277-281. doi:
38 453 10.3109/00365597709179965
- 39 454 [27] Gez E, Libes M, Bar-Deroma R, et al. Postoperative irradiation in localized renal cell
40 455 carcinoma: the Rambam Medical Center experience[J]. *Tumori*, 2002, 88(6): 500-502. doi:
41 456 [28] Deschavanne PJ, Fertil B. A review of human cell radiosensitivity in vitro[J]. *Int J Radiat*
42 457 *Oncol Biol Phys*, 1996, 34(1): 251-266. doi: 10.1016/0360-3016(95)02029-2
- 43 458 [29] Dengina N, Tsimafeyeu I, Mitin T. Current Role of Radiotherapy for Renal-Cell Carcinoma:
44 459 Review[J]. *Clin Genitourin Cancer*, 2017, 15(2): 183-187. doi: 10.1016/j.clgc.2016.09.004
- 45 460 [30] Lo SS, Slotman BJ, Lock M, et al. The development of stereotactic body radiotherapy in
46 461 the past decade: a global perspective[J]. *Future Oncol*, 2015, 11(19): 2721-2733. doi:
47 462 10.2217/fon.15.220
- 48 463 [31] Kann BH, Miccio JA, Stahl JM, et al. Stereotactic body radiotherapy with adjuvant systemic
49 464 therapy for early-stage non-small cell lung carcinoma: A multi-institutional analysis[J].
50 465 *Radiother Oncol*, 2019, 132: 188-196. doi: 10.1016/j.radonc.2018.10.017

- 1
2
3 466 [32] Margulis V, Freifeld Y, Pop LM, et al. Neoadjuvant SABR for Renal Cell Carcinoma Inferior
4 467 Vena Cava Tumor Thrombus-Safety Lead-in Results of a Phase 2 Trial[J]. *Int J Radiat*
5 468 *Oncol Biol Phys*, 2021, 110(4): 1135-1142. doi: 10.1016/j.ijrobp.2021.01.054
6
7 469 [33] Siva S, Louie AV, Warner A, et al. Pooled analysis of stereotactic ablative radiotherapy for
8 470 primary renal cell carcinoma: A report from the International Radiosurgery Oncology
9 471 Consortium for Kidney (IROCK)[J]. *Cancer*, 2018, 124(5): 934-942. doi:
10 472 10.1002/cncr.31156
11 473 [34] Siva S, Ellis RJ, Ponsky L, et al. Consensus statement from the International Radiosurgery
12 474 Oncology Consortium for Kidney for primary renal cell carcinoma[J]. *Future Oncol*, 2016,
13 475 12(5): 637-645. doi: 10.2217/fon.16.2
14 476 [35] Valero G, Luján JA, Hernández Q, et al. Neoadjuvant radiation and chemotherapy in rectal
15 477 cancer does not increase postoperative complications[J]. *Int J Colorectal Dis*, 2003, 18(6):
16 478 495-499. doi: 10.1007/s00384-003-0520-1
17
18 479 [36] Li Y, Lin J, Xiao J, et al. Therapeutic effects of Co-Venenum Bufonis Oral Liquid on
19 480 radiation-induced esophagitis in rats[J]. *Exp Anim*, 2020, 69(3): 354-362. doi:
20 481 10.1538/expanim.19-0142
21 482 [37] Lee SR, Yang KA, Kim SK, et al. Radiation-induced intratumoral necrosis and peritumoral
22 483 edema after gamma knife radiosurgery for intracranial meningiomas[J]. *J Korean*
23 484 *Neurosurg Soc*, 2012, 52(2): 98-102. doi: 10.3340/jkns.2012.52.2.98
24
25 485 [38] Almohammad F, Bakour MM. Solitary fibrous renal tumor with thrombus extension into the
26 486 inferior vena cava and right atrium[J]. *Asian Cardiovasc Thorac Ann*, 2021, 29(8): 813-815.
27 487 doi: 10.1177/0218492321997391
28 488 [39] Chirieac LR, Swisher SG, Correa AM, et al. Signet-ring cell or mucinous histology after
29 489 preoperative chemoradiation and survival in patients with esophageal or esophagogastric
30 490 junction adenocarcinoma[J]. *Clin Cancer Res*, 2005, 11(6): 2229-2236. doi: 10.1158/1078-
31 491 0432.Ccr-04-1840
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 Figure 1. Flowchart for minimum assessments during treatment and follow up phase
4
5
6

7 Figure 2. Schematic outline of the treatment plan. Patients with renal cell carcinoma with Mayo II-IV
8 tumor thrombus will finish radiotherapy for thrombus area (total 30Gy). Radical nephrectomy and
9 thrombectomy will be performed between week 7~8. Follow up for secondary endpoints will be starting
10 at the date of nephrectomy and thrombectomy for 1 year every 3 months.
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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)

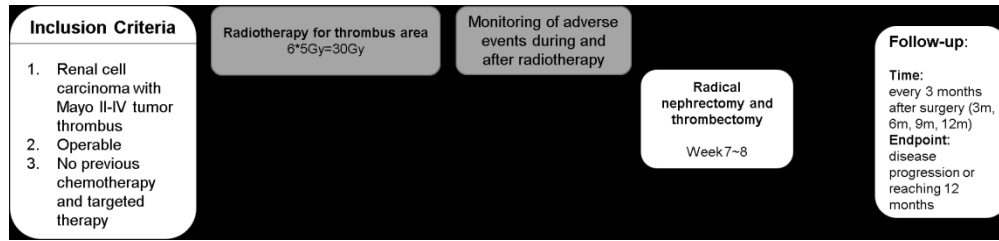


Figure 2. Schematic outline of the treatment plan. Patients with renal cell carcinoma with Mayo II-IV tumor thrombus will finish radiotherapy for thrombus area (total 30Gy). Radical nephrectomy and thrombectomy will be performed between week 7~8. Follow up for secondary endpoints will be starting at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

314x73mm (150 x 150 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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 \geq 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

1
2
3 treatment for renal cell carcinoma with inferior vena cava tumor thrombus.

4 The research unit has all the diagnostic and therapeutic conditions involved in the protocol.
5 The level of urology surgery in our hospital is in the lead in China. There are a group of clinical
6 experts specialized in renal cell carcinoma with inferior vena cava tumor thrombus, who can ensure
7 that the enrolled patients receive standard preoperative radiotherapy and surgical treatment.
8
9

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

11 To determine the safety of the treatment by the study of preoperative stereotactic radiotherapy
12 combined with surgical treatment of patients with renal cell carcinoma and inferior vena cava tumor
13 thrombus. Main purpose: 1. To identify the acute and late toxicity of radiotherapy. Severe toxicity
14 is defined as grade III-IV toxicity according to Common Terminology Criteria Adverse Events
15 (CTCAE) v4.0. 2. To identify whether the difficulty or risk of surgery is increased after radiotherapy
16 by analyzing perioperative complications, operation time, intraoperative bleeding volume,
17 intraoperative transfusion volume of suspended red blood cells, and postoperative hospital stay.
18 Secondary purpose: Using the follow-up data of the patients to clarify the curative effect of the
19 treatment: 1. For Mayo III-IV classification, it may reduce the difficulty of operation, blood loss,
20 blood transfusion rate and perioperative complications. 2. For Mayo II-IV classification,
21 preoperative radiotherapy + surgery may be better than surgery alone, which prolongs survival and
22 reduces recurrence rate. 3. When the tumor thrombus invades the inferior vena cava wall in a wide
23 range, preoperative radiotherapy can be used to preserve the inferior vena cava vessel wall. The
24 pathological changes of tumors after radiotherapy have been proved to have prognostic significance
25 in other tumors. Tumors such as rectal cancer have clear grading standards, which are divided into
26 4 grades according to the degree of residual tumor after radiotherapy. This study attempts to initially
27 explore the post-radiotherapy changes of renal tumor thrombus, and judge the prognosis of the
28 tumor according to the different pathological changes.
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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 trial 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.

1
2
3 (II) Inclusion and exclusion criteria

4 Inclusion criteria:

- 5 1) Age \geq 18 years old.
6 2) Imaging examination of renal cell carcinoma with inferior vena cava tumor thrombus.
7 3) Inferior vena cava tumor thrombus graded from Mayo II to Mayo IV.
8 4) Oncologists believe that patients are suitable for preoperative stereotactic ablative body
9 radiotherapy (SABR) to treat inferior vena cava tumor thrombus.
10 5) Urologists believe that patients are suitable for radical nephrectomy and inferior vena cava
11 thrombectomy to treat renal cancer and inferior vena cava tumor thrombus.
12 6) ECOG 0-2.
13 7) Able to complete enhanced CT or enhanced MRI (either one) examination.
14 8) Able to sign this Informed Consent Form.

15 Exclusion criteria:

- 16 1) Subjects with a history of radiotherapy in the area of renal cell carcinoma or inferior vena
17 cava tumor thrombus.
18 2) Subjects with a history of preoperative targeted therapy, preoperative chemotherapy, or
19 other related treatments.
20 3) Subjects with a history of pulmonary embolism.
21 4) Subjects with severe cardiopulmonary insufficiency, severe arrhythmia, myocardial
22 infarction, angina pectoris, severe coagulation disease, or severe liver disease that cannot tolerate
23 SABR or surgery.
24 5) Subjects with diseases that severely affect the judgment of patients, such as mental disorders.

25 (III) Research process

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

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

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

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

35 The research content process of this project:

- 36 (1) On the 1st day after admission, you will have a pre-radiotherapy location check to complete the
37 pre-radiation preparations;
38 (2) On the 2-7 days after admission, you will have preoperative radiotherapy;
39 (3) After 4-6 weeks of rest, on the 1st day of re-admission you will have blood routine test, blood
40 biochemistry test, urine routine test, coagulation function test, enhanced CT of the urinary system,
41 and enhanced MRI of the inferior vena cava;

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

- 1
2
3 (4) On the 3rd day of re-admission, complete the pre-operation preparations;
4 (5) On the 4th day of re-admission, you will receive routine surgical treatment;
5 (6) On the 1st day after surgery, you will have blood routine, blood biochemistry, urine routine,
6 erythrocyte sedimentation rate, and coagulation function tests to complete the assessment of your
7 recovery after the operation. At the same time, you will receive conventional intravenous medication
8 after surgery.
9
10 (7) On the 2nd day after surgery, you will have blood routine, blood biochemistry, urine routine,
11 erythrocyte sedimentation rate, and coagulation function tests to complete the assessment of your
12 recovery after the operation. At the same time, you will receive conventional intravenous medication
13 after surgery.
14
15 (8) On the 3rd day after the operation, you will have blood routine, blood biochemistry, urine routine,
16 erythrocyte sedimentation rate, and coagulation function tests to complete the assessment of your
17 recovery after the operation. At the same time, you will receive conventional intravenous medication
18 after surgery.
19
20 (9) On the 7th day after surgery, you will have blood routine, blood biochemistry, urine routine,
21 erythrocyte sedimentation rate, and coagulation function tests to complete the assessment of your
22 recovery after the operation.
23
24 (10) On the day of discharge after surgery, you will have blood routine, blood biochemistry, urine
25 routine, erythrocyte sedimentation rate, and coagulation function tests to complete the assessment
26 of your recovery after the operation.
27
28 (11) Every day after the operation, a urology doctor with a title of deputy chief or above will conduct
29 ward rounds to closely observe your condition. Your postoperative pathology will be evaluated by
30 a professional pathologist;
31
32 (12) 3 months, 6 months, 9 months, and 12 months after surgery, please go to the outpatient clinic
33 for follow-up in time, and we will also conduct a telephone follow-up.
34
35
36

37 3. For the study of discarded tissues after routine clinical surgery / operation: our research
38 materials are from discarded tissues after routine clinical surgery / operation, and the enrollment test
39 will not expand the scope of your surgery / operation, nor will it increase the number of specimens.
40
41

42 4. Drugs or procedures prohibited in the study:

43 None.
44
45

46 5. What do I need to do to participate in the research?

47 You must come to the hospital with a copy of the medical record and the medical follow-up
48 form according to the follow-up time agreed by the doctor and yourself (during the follow-up period,
49 the doctor may know your situation by telephone or on-site). Your follow-up is very important
50 because the doctor will judge whether the treatment you received really works and guide you in
51 time.
52
53

54 According to your condition, if you need to take medicines related to renal cancer treatment
55 after surgery, you must follow the instructions of your doctor, and please fill in your medication
56 records in a timely and objective manner. At each follow-up, you must return the unused medicines
57 and their packages, and bring other medicines you are taking, including those that you must continue
58 to take if you have other comorbid diseases.
59
60

1
2
3 You cannot use other medicines for kidney cancer during the study period. If you need other
4 treatments, please contact your doctor in advance.
5
6

7 (IV) How long will this research last?

8 3 months, 6 months, 9 months, and 12 months after surgery, please go to the outpatient clinic for
9 follow-up in time. We will also conduct a 2-year telephone follow-up based on your condition.

10 You can decide to withdraw from the study at any time without losing any benefits you should have
11 received. However, if you decide to withdraw during the course, taking into account your safety
12 issues, it is possible that a related medical examination will be carried out after withdrawal.
13
14

15
16 (V) What are the risks of participating in this study?

17 In addition to the risks in the conventional treatment process (before taking a certain treatment
18 measure, we will explain the risks of the treatment in detail and sign an additional informed consent
19 form with you), participating in this study may have the following risks. At the same time, we have
20 prepared the relevant treatment plan and possible compensation plan:
21

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

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

25 (3) During radiotherapy, the tumor thrombus may become loose, and the proximal end may fall off
26 to the heart, which may cause pulmonary embolism and threaten life, and pulmonary embolectomy
27 may be required.
28

29 (4) There may be undiscovered or unpredictable adverse events.
30
31

32
33 Solution:

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

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

37 (3) If spinal cord injury occurs, it may require diuresis, detumescence, cortisol hormone therapy,
38 and surgery if necessary.
39

40 (4) If radiotherapy-related toxicity occurs, we treat it symptomatically.
41

42 If you experience any discomfort or new changes in your condition during the study period, or
43 any unexpected situation, regardless of whether it is related to the study, you should notify your
44 doctor in time, and he/she will make judgment and give appropriate medical treatment.
45

46 During the study period, you need to go to the hospital on time for follow-up and examinations,
47 which may take up some of your time and may cause trouble or inconvenience to you.
48

49 For female subjects:

50 During the study period, pregnancy brings great risks to unborn children, some of which are
51 unpredictable at present. Therefore, pregnant women will not be recruited as subjects in this study.

52 If you are in childbearing age (including one year after amenorrhea), you will be tested for
53 pregnancy (venous blood should be taken for examination), and the test result must be negative
54 before you can continue to participate in this study. If you have sex, you must agree to take
55 appropriate contraceptive measures during the course of the study and in the following months. If
56 you are pregnant or have unprotected sex during the study, please inform your research doctor
57 immediately.
58
59
60

1
2
3 For male subjects:

4 Participation in this study may damage your sperm and the children you gave birth to during the
5 study. The damage is currently unpredictable. If you have sex, you must agree to use medically
6 approved contraception during the course of the study and in the following months. Please inform
7 your partner of this risk to the unborn baby. She should understand that if she is pregnant, you need
8 to inform your research doctor immediately, and she should also inform her doctor immediately.
9

10
11
12 (VI) Drug interactions:

13 For safety reasons, you must inform the research doctor or nurse of all prescription drugs, traditional
14 Chinese medicine products, over-the-counter drugs, vitamins, natural supplements and other health
15 products you are taking before the start of the study. Be sure to tell your research doctor or nurse
16 before taking these drugs during the study.
17
18
19

20 21 22 **IV. What are the benefits of participating in the research?**

23
24
25 If you agree to participate in this study, you may have direct medical benefits. For example: 1.
26 Reduce the difficulty of operation, blood loss, blood transfusion rate and perioperative
27 complications; 2. In this study, preoperative stereotactic radiotherapy (SBRT) as an adjuvant
28 surgery may be better than surgery alone, which may prolong the survival time and reduce the
29 recurrence rate; 3. When the tumor thrombus invades the wall of inferior vena cava in a wide range,
30 preoperative radiotherapy can be used to preserve the wall of inferior vena cava.
31

32 We hope that the information obtained from your participation in this study will benefit patients
33 with the same condition as yours in the future.
34

35 Although there is already evidence that radiotherapy has a satisfactory effect on patients with
36 renal cell carcinoma and tumor thrombus, it can not guarantee that it will be effective for you, and
37 you may not have the above benefits. The preoperative stereotactic radiotherapy (SBRT) is not the
38 only way to treat renal cell carcinoma with venous tumor thrombus. If preoperative stereotactic
39 radiotherapy (SBRT) is not effective for your condition, you can ask your doctor about possible
40 alternative treatment.
41
42
43
44
45

46 47 **V. Alternative medical options?**

48
49 If you do not participate in this study, you have the following options:

- 50 ● Surgery alone
- 51 ● Radiotherapy alone
- 52 ● Surgery combined with postoperative adjuvant therapy (radiotherapy, chemotherapy,
53 targeted therapy, etc.)
- 54 ● Palliative treatment
- 55
- 56
- 57
- 58
- 59
- 60

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

1
2
3 withdraw from the study at any time without any reason; I have informed the subject that he / she
4 will receive a copy of this informed consent form, which contains my signature and his / her
5 signature.”
6
7

8 Signature of the researcher who obtained the informed consent _____

9 Contact telephone number _____

10 Date _____
11
12
13

14 15 **XIV. Informed consent statement**

16
17
18 “I have been informed of the background, purpose, procedures, risks and benefits of the clinical
19 study on the safety and effectiveness of neoadjuvant stereotactic radiotherapy combined with
20 surgical treatment for patients with renal cell carcinoma with inferior vena cava tumor thrombus. I
21 have enough time and opportunity to ask questions, and I am very satisfied with the answers. I have
22 also been told who I should contact when I have questions, dissatisfaction, concerns or want further
23 information. I have read this informed consent and agree to participate in this study. I promise that
24 the information and test results provided to the researchers are true and valid. I know that I can
25 withdraw from this study at any time without any reason. I have been told that I will be given a copy
26 of this informed consent form, which contains the signatures of me and the researcher.”
27
28
29
30

31 Signature of the subject _____

32 Contact telephone number _____

33 Date _____
34
35
36
37
38

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

40
41 The relationship between the legal representative and the subject: _____

42 Signature of the legal representative _____

43 Contact telephone number _____

44 Date _____
45
46
47

48 Press the fingerprint:
49
50
51
52
53
54
55
56
57
58
59
60