Research Square

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Robotic radical antegrade modular pancreatosplenectomy(RAMPS) versus standard retrograde pancreatosplenectomy (SRPS):study protocol for a randomized controlled trial

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Study protocol

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Abstract

Abstract Background There has been data from meta-analysis suggesting that RAMPS is a safe and effective procedure for adenocarcinoma in the body or tail of the pancreas and is oncologically superior to SRPS. However, previous studies on RAMPS were conducted under the open and laparoscopic surgery. Robotic surgery, on the other hand, plays a role in ergonomics and offers several advantages, including less fatigue, tremor filtering, 7° of wrist-like motion, motion scaling, and three-dimensional vision. At present, there is still a lack of clinical studies to observe the safety and clinical efficacy of Robotic RAMPS in the world. Hence,prospective randomized controlled trials (RCTs) comparing Robotic RAMPS and SRPS are required. We begin a RCT trial to compare short-term surgical and oncological outcomes of Robotic RAMPS and SRPS for patients with distal pancreatectomy.Methods This is a randomized, single-center clinical trial. All included adults are patients with primary carcinoma of the distal pancreatectomy. A total of 246 patients will be randomly allocated to Robotic RAMPS or SRPS. The primary endpoints are oncological outcomes(R0 rate, number of Lymph node). Secondary endpoints are the perioperative complications, Perioperative indicators(operative time,blood loss,blood transfusion volume,costs).Discussion To evaluate the surgical and oncological outcomes of Robotic RAMPS, we therefore undertake a prospective RCT. This procedure may become a standard approach to robotic pancreatosplenectomy.

Introduction

Background and rationale {6a}

Early diagnosis of pancreatic cancer is difficult, and the prognosis of patients is extremely poor, with a 5-year survival rate of only about 5%**[1]**. Complete surgical resection is the only possible cure for pancreatic cancer, and R0 resection is the most important factor affecting postoperative survival of patients**[2-4]**. Therefore, how to improve the rate of R0 resection in pancreatic surgery, delay and reduce local recurrence, has been a hotspot of pancreatic surgery research.

The positive rate of peritoneal resection margin was high after SRPS, which was an important cause of tumor metastasis and recurrence. With the progress of the concept of tumor treatment, the surgical method of pancreatic body and tail cancer has been improved. Strasberg et al. proposed RAMPS in 2003. Due to its theoretical rationality and good surgical effect, it has attracted the attention of pancreatic surgeons. It is expected to be the standard operation for distal pancreatectomy**[5]**.

RAMPS focus on radical resection at the resection margin of the retroperitoneum. According to whether the tumor invaded the posterior capsule of the pancreas, the anterior approach or the posterior approach were used to improve the R0 resection rate of the resection margin of the retroperitoneum and the effect of radical resection of the tumor. It was reported a few years ago that, compared with SRPS, RAMPS showed significant improvement in R0 resection rate and 5-year survival rate**[5, 6] .** However, reports in recent years have shown that despite the theoretic advantages of RAMPS over SRPS, high-level evidence

that demonstrates a survival benefit with RAMPS does not currently exist**[7, 8]**. RAMPS 'potential survival advantage still needs to be proven.

The robot surgical system plays an essential role in ergonomics and offers advantages, such as less fatigue, tremor filtering, 7° of wrist-like motion, motion scaling, and three-dimensional vision**[9-12]**. These characteristics make robots have advantages in delicate operation, small space, complex reconstruction and operation involving blood vessels. Robotic surgery is becoming the mainstream of urology, gynecology and other abdominal surgery in the future**[13, 14]**.

Objectives {7}

The aim of our study is to compare the safety and prognosis with robotic RAMPS and SRPS in the treatment of pancreatic body and tail cancer.

Trial design {8}

This study is a single-center randomized controlled study in which patients will be assigned randomly into control and trial groups.

Methods

Participants, interventions and outcomes

Study setting {9}

From August ,2019 to September 31, 2022, patients will be selected from the Chinese People's Liberation Army General Hospital (CPGH) for treatment. All patients were diagnosed with pancreatic body and tail cancer and met the inclusion criteria. A total of 256 patients were scheduled to be included in the study. After confirmation of the eligibility criteria, including written informed consent, registration is made to the central registry in CPGH. Each patient will be randomly assigned a number in the central registry. Then patients are randomized in a 1:1 allocation ratio to either arm A (RAMPS) or arm B (SRPS) with a random block size. (Fig.1)

Eligibility criteria {10}

Inclusion criteria

1. Obtain informed consent signed by the patient or his or her legal agent;
2. Compliance with the study plan and follow-up procedure;
3. Aged 18 to 70 years old male and female;
4. No surgical contraindications, able to tolerate radical surgery, ECOG behavioral status score 0-1, life expectancy ≥ 12 weeks, ASA score ≤ 2;

5. The tumor was diagnosed as resectable by preoperative pathological examination or clinical judgment
6. It meets the indications of resection of pancreatic somatococcygeal carcinoma by robot;

Exclusion criteria

1. Malignant tumors in other areas within the last 5 years;
2. Patients with brain, lung, bone metastases or abdominal lymph node metastases;
3. Patients with severe cardiopulmonary function, liver and renal function infection;
4. Women during pregnancy or lactation

Participating surgeons

Differences in the surgical experience of surgeons may lead to differences in the incidence of complications. By analyzing the perioperative data of the first 100 cases of robotic pancreaticoduodenectomy performed by a single surgeon in our center, we found that 40 cases could span the learning curve after surgery. The postoperative operation time, intraoperative blood loss and complications of the patients were significantly decreased**[15]**. In this research, our surgical team consists of three doctors and each of these clinicians meet the participation requirements and received adequate training prior to participating in the study. Patients will be randomly assigned to each doctor's surgery group.

Who will take informed consent? {26a}

The surgeon Dr Liu will recruit the patient when discussing treatment with the patient using pancreatosplenectomy. Patients will be selected from the Chinese People's Liberation Army General Hospital (CPGH) for treatment from August ,2019 to September 31, 2022. The trial was consistent with the principles of the Declaration of Helsinki and in accordance with the Medical Research Involving Human Subjects Act (WMO), and has been approved by the medical ethics committee of the CPGH. To protect the privacy of the subjects, data are processed anonymously. Written informed consent for the study will be obtained from each patient before surgery.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

On the consent form, if the participant opts out of the trial, the participant is asked if he or she agrees to use their data. Participants will also be required to allow the research team to share relevant data with people from the university or relevant authorities.

Interventions

Explanation for the choice of comparators {6b}

Previous studies on RAMPS were conducted under laparotomy and laparoscopy. There is still a lack of clinical studies on the safety and clinical efficacy of robotic RAMPS in the world. We meditate to conduct an RCT to compare short-term surgical oncological outcomes between robotic RAMPS and robotic SRPS for patients with distal pancreatectomy. Through this study, we wanted to find out whether RAMPS performed better than SRPS in robotic surgery.

Intervention description {11a}

Surgical technique

Robotic radical antegrade modular pancreatosplenectomy

All RDP procedures will be performed using the da Vinci™ Si Surgical System (Intuitive, Sunnyvale, CA, USA). After the general anesthesia is effective, the patient is placed in a supine position. Our surgical procedures of RDPS and LDPS have been described previously[16, 17]. The layout of Trocar is shown in Fig.2[18]. Diagnostic laparoscopy is performed to rule out metastasis. Open gastric colon ligament and separate the superior mesenteric vein at the lower margin of the pancreatic neck. The little omentum capsule is then opened to dissect the common hepatic artery, and para-hepatic arterial lymph nodes are dissected (groups 8a and 8p). The gastroduodenal artery is isolated, and then the superior portal vein of the pancreas is exposed. Establish the pancreatic neck tunnel and disconnect the pancreatic neck. Lymph nodes around the celiac trunk (9 groups) and fibrous adipose tissue are dissected. The splenic artery is isolated along the celiac trunk, ligate and sever in the root, and the left gastric artery is severed when necessary. The distal pancreas is pulled from right to left, the splenic vein is severed from the root, and the proximal end is closed with 5-0prolene continuous suture. Lymph nodes are dissected downward from the celiac trunk and the periceliac nerve plexus to the superior mesenteric artery, and the left lymph node of the superior mesenteric artery is dissected (group 14c and group 14d). Continue dissecting posteriorly and reveal the leading edge of the left renal vein and left adrenal vein. The specimen is redirected to the left to ensure that the anatomical resection plane is located behind Gerota's fascia. The anterior approach should be close to the left renal vein, renal capsule and the front edge of the left adrenal surface to clear the retroperitoneal tissue (this is the anterior RAMPS). The posterior approach requires resection of the left adrenal gland and its surrounding tissue (posterior RAMPS). At the same time, the upper and lower edges of the pancreas are freed, and then the ligaments around the spleen are removed, and the specimen is finally removed.

Robotic standard retrograde pancreatosplenectomy

Anesthesia and trocar are arranged as RAMPS described above. Open the colon ligaments and then separate the spleen-stomach ligaments, the splenic-colonic ligaments, and the splenic-diaphragmatic ligaments to free the spleen. The pancreas is separated from the retroperitoneum from the left to the right and disconnect the pancreas about 2 cm away from the distal end of the tumor. Then suture pancreatic stump to stop bleeding.

Intra-abdominal drainage

A drainage tube will be placed to assess the PF as the primary endpoint before the abdomen is closed. The number and location of the inserted drainage tubes will be recorded in the data sheet. And we will specify when to remove the drain.

Criteria for discontinuing or modifying allocated interventions {11b}

The rejection and withdrawal criteria :

(1) it does not meet the inclusion criteria of the study;(2) the clinical data obtained after inclusion is incomplete, and further clinical statistical analysis cannot be conducted;(3) the subjects experienced serious adverse events/reactions related to the treatment regimen, and the investigator considered it necessary to withdraw them from the trial;(4) during the trial, the patient's condition continued to deteriorate and dangerous events might occur, so the researcher considered it necessary to withdraw him from the clinical trial;(5) patients who voluntarily withdrew during the trial - all patients who completed the informed consent and were eligible to participate in the trial at screening, regardless of when or where they withdrew, were classified as dropout cases. They did not complete the observation period specified in the agreement;(6) poor treatment compliance affects the determination of efficacy and safety.

Strategies to improve adherence to interventions {11c}

Concurrent and supportive treatments

Adherence is not an issue for patients as this is a surgical trial. We will check the surgeon's operation with the surgical record after the operation.

Relevant concomitant care permitted or prohibited during the trial {11d}

The surgeon will determine the use of antibiotics, blood products, analgesics, H2 blockers, and proton pump inhibitors based on perioperative management. Octreotide will be routinely applied to prevent pancreatic fistula. Abdominal ultrasonography will be performed regularly to determine the presence of peritoneal effusion. The serum amylase and bilirubin will be measured regularly in the drainage fluid of the abdominal drainage tube after operation. Implementing robotic RAMPS or robotic SRPS will not require alteration to usual care pathways and these will continue for both trial arms.

Provisions for post-trial care {30}

There is no anticipated harm and compensation for trial participation.

Outcomes {12}

Endpoints

The primary efficacy endpoint of the trial will be the rates of resection margins. In the case of malignant pancreatic disease, resection margins are classified by a margin to tumor distance ≥1 mm (R0), a margin to tumor distance <1 mm (R1) or a macroscopically positive margin (R2)[19]. The second endpoints are: (1)the number of lymph node.(2) retrieval postoperative complications including pancreatic fistula, intra-abdominal abscess, and anastomotic leakage, according to the Clavien-Dindo classification（Table.1）. Complications higher than grade II are regarded as clinically significant[20]; (3) perioperative indicators; such as operation time, blood loss, blood transfusion volume, transition rate to open surgery, postoperative hospitalization days, hospital costs.

Participant timeline {13}

An independent research physician will not be involved in the treatment and monitoring of patients in the surgical room and enter all necessary data into the prepared CRF. The CRF will be completed as soon as possible, preferably on the day of patient treatment and visit (Table. 2). Reasonable explanations should be given for all missing data. The complete CRF page will be examined for completeness and reasonableness by the principal investigator and responsible supervisors.

Sample size {14}

Determination of the marginal resection rate is the main endpoint of this study. Published literatures with large sample size (n > 100) of distal adenocarcinoma demonstrate R0 resection rate of 50%–74%[21, 22]. A systematic review of radical antegrade modular pancreatosplenectomy which identified 13 observational studies involving 354 patients undergoing RAMPS showed that the R0 resection rate was 88% [23] . According to these studies, we used a two-sided log-rank test which requires about 23-123 patients in each group with 80% power at the 0.05 level of significance (NCSS and PASS 11 (NCSS Statistical Software, Kaysville, UT, USA)). Considering that there is a large gap in the estimated quantity of samples, we plan to collect 90 samples in each group . Considering a drop-out rate of 10%, a total sample size of total sample size required is n = 200 patients. After 50 samples were collected in each group, we will make a mid-term comparison to determine whether there are significant differences in the results. Based on the results, we decide whether or not to conduct the next data collection.

Recruitment {15}

Because we are a top hospital in China, we believe we can collect enough patient data in enough time

Assignment of interventions: allocation

Sequence generation {16a}

Each patient will be assigned a computer-generated random number in the central registry.

Concealment mechanism {16b}

Then patients are randomized in a 1:1 allocation ratio to either arm A (RAMPS) or arm B (SRPS) with a random block size. (Fig.1)

Implementation {16c}

The central registry in CPGH will generate the allocation sequence, enrol participants and assign participants to interventions.

Assignment of interventions: Blinding

Who will be blinded {17a}

The experiment was a single blind trial. Patients will not know their grouping. Surgeons perform operations according to their group

Procedure for unblinding if needed {17b}

After the patient is discharged from hospital, we will send the patient's surgical procedure in the form of medical records.

Data collection and management

Plans for assessment and collection of outcomes {18a}

The data manager will use two input methods to enter data from the CRF table into the ResMan database. The inspector will examine each item in the database, report inconsistent result values, validate each item in the original questionnaire, and make corrections as necessary.

Plans to promote participant retention and complete follow-up {18b}

Not applicable.

Data management {19}

The CPGH will be responsible for data management and statistical analysis of the study. The corresponding tables of codes and informed consent forms will be kept strictly in the CPGH file library. All required parameters will be collected in SPSS data files (SPSS version 25, IBM statistics, Chicago, IL, USA).

Confidentiality {27}

Participants' medical records will be kept at the hospital. Researchers, research institutions and ethics committees will be allowed access to the records. The study will not reveal the individual identities of the participants. Participants can request access to their personal information (such as address, contact information, etc.) at any time and can modify this information if necessary.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

In this trial we will collect blood and drainage fluid samples from patients for laboratory testing.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

Statistical analysts do not participate in clinical observation. They will be blinded to allocation and responsible for statistical analysis of research data and timely delivery of statistical reports to the research director. All analyses will be performed and reported in accordance with the CONSORT statement and the ICH E9 'Statistical Principles in Clinical Trials'. Primary and secondary outcomes will be cross-checked against data. The measurement data are expressed as mean ± standard deviation. The normality test and homogeneity test of variance will be performed first. To compare normally distributed continuous variables, the independent sample t-test will be used, and the values will be represented as the mean with standard deviation. Continuous non-normally distributed variables will be compared using the Mann-Whitney U test, whose values will be expressed as the median of the quartile spacing. The categorical variables are compared using the chi-square test or the Fisher's exact test, and values will be expressed as proportions with corresponding risk ratios and 95% confidence intervals. $P < 0.05$ indicates statistical significance. Statistical analysis will be performed using SPSS 20.0 software.

Interim analyses {21b}

A statistical analysis will be performed when the total number of samples collected reaches 100. Primary investigator will obtain these interim results and decide whether to continue the experiment. We will discontinue the trial if the safety of the RAMPS surgery group is much lower than that of the control group in the outcome of the interim data.

Methods for additional analyses (e.g. subgroup analyses) {20b}

We plan to do subgroup analysis by gender or surgeon undertaking the operations in the future.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

We will exclude patients who do not receive the intervention and whose primary data are missing.

Plans to give access to the full protocol, participant level-data and statistical code {31c}

The full protocol is available on request from the corresponding author.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee {5d}

The data monitoring committee (DMC) consists of principals, data managers, data monitors, and statistical analysts. It is independent from the sponsor and competing interests

Composition of the data monitoring committee, its role and reporting structure {21a}

During the study, DMC will be established to conduct periodic interim evaluations and, where appropriate, to optimize the study based on the results of the interim evaluations. When there are obvious differences such as the safety gap between the two groups of experiments, DMC is authorized to discontinue the trial.

Adverse event reporting and harms {22}

Any adverse medical events that occur in subjects during the observational clinical study are considered adverse events (AE).Complications resulting from surgery, such as pancreatic fistula, postoperative bleeding, and death, are considered serious adverse events and are reported to the medical supervisor.AE report forms will be filled out during the trial period. Record the timing, severity, duration, actions taken and outcome of adverse events.

Frequency and plans for auditing trial conduct {23}

During the implementation of the project, DMC will conduct regular or irregular review and random inspection of the original test data and check the compliance of the study.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) {25}

When major changes occur in the study process, we will first notify the sponsor, then principal investigator (PI) will notify the centres and that a copy of the revised protocol will be sent to PI to add to the Investigator Site File. Any deviations from the Protocol will be fully documented using a breach report form. Then we will update the protocol in the clinical trial registry.

Dissemination plans {31a}

After all data have been collected and counted. We will publish the results in the journal.

Discussion

In 1882, Trendelemburg completed the world's first tail resection of the pancreas[24]. MAYO standardized the procedure in 1913. In this way, the spleen was gradually removed from the left to the right, and the pancreas was gradually severed to remove the lesion [25]. But this type of surgery has disadvantages. During the process of resection, the tumor may be squeezed, causing metastasis or recurrence of the tumor.

In 2003, Strasberg modified the traditional pancreatic tail resection. The pancreatic neck was first separated and the superior mesenteric arteries and veins, splenic vessels and celiac trunk were exposed. The corresponding lymph nodes were then dissected and the splenic vessels were severed. The tumor and spleen were resected from right to left at last. This operation mode can be in line with lymph node drainage mode to clean lymph nodes, and can achieve "no-touch" of tumor resection, so as to improve the incidence of tumor resection of R0[5].

There have been some studies comparing the advantages and disadvantages of SRPS and RAMPS, suggesting that RAMPS is safe and feasible [26]and has a better R0 resection rate than traditional tail pancreatectomy (70%-80%)[27]. In the system evaluation of Zhou in 2017, 13 clinical studies including 354 patients with RAMPS were included, and the R0 resection rate reached 88%, and the 5-year survival rate reached 37%. Compared with SRPS, it has less bleeding, more lymph node dissection and higher R0 resection rate [23].

But there has been a lack of studies comparing the two approaches to robotic surgery. To evaluate the surgical and oncological outcomes of robotic RAMPS, we therefore undertake a prospective RCT. This procedure may become a standard approach to robotic pancreatosplenectomy. In this way, the most beneficial technique can be selected for individual patients.

Trial status

We are currently recruiting participants. The latest version is version 2.0 on August 10, 2019.The first participant was recruited on September 6, 2019, and the recruitment is expected to be completed in December 2020.

Abbreviations

AE	Adverse events
CPGH	Chinese People's Liberation Army General Hospital
CRF	Clinical report form
OS	Overall survival
PI	Principal investigator
RAMPS	Radical antegrade modular pancreatosplenectomy
RCT	Randomized controlled trial
RFS	Relapse-free survival
SRPS	Standard retrograde pancreatosplenectomy
AE	Adverse events

Declarations

Acknowledgements

Not applicable

Authors' contributions {31b}

Gong Zhang and Rong Liu conceived the study conception and design, drafted of the manuscript, and critical revision of the manuscript. Kangyu Hao performed the statistical analysis. Haifeng Zhang calculated the sample size. Fei Wang assisted in the evaluation and revision of the agreement and the revision of the manuscript. All authors read and approved the final version of the manuscript.

Funding {4}

Department of Hepatobiliary and Pancreatic Surgical Oncology, Chinese People's Liberation Army (PLA) General Hospital . This finding is conducted without outside funding.

Availability of data and materials {29}

Data sets used or analyzed in the current study may be provided upon reasonable request of the corresponding author.

Ethics approval and consent to participate {24}

The trial was consistent with the principles of the Declaration of Helsinki and in accordance with the Medical Research Involving Human Subjects Act (WMO). Written informed consent for the study will be obtained from each patient before surgery. The research was approved by CPGH's ethics review committee (approval number: S-2016-098-02). This study was registered on the Chinese Clinical Trial Registry (ID：ChiCTR1900020833).

Consent for publication {32}

These are available on request from the corresponding author.

Competing interests {28}

The authors declare that they don't have competing interests.

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Study conception and design: Rong Liu，Gong Zhang. Drafting of the manuscript: Gong Zhang，YuHao Kang ，Haifeng Zhang. Critical revision of the manuscript: Fei Wang. All authors have read and approved the final version of the manuscript.

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Tables

Table.1 Complication grades according to the Clavien-Dindo classication schemea

Grade	Definition
V	Death of patient
IV	Life-threatening complication. Requiring intensive care unit management
IVa	Single organ dysfunction
IVb	Multi-organ dysfunction
III	Requiring surgical, endoscopic, or radiological intervention
IIIa	Intervention not under general anesthesia
IIIb	Intervention under general anesthesia
II	Requiring pharmacological treatment with drugs other than those allowed for grade I complications
I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological intervention

Table. 2 Flow chart of the trial

	Screening					
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 5
	Before surgery	Day of surgery	POD 1[b]	POD 3	POD 7	POD 30
Informed consent	x					
Personal data	x					
Physical examination	x					
Previous medical history	x					
Inclusion / Exclusion criteria	x					
CT/MRI	x					
Blood tests	x		x	x	x	x
Trial intervention		x				
Intraoperative outcomes		x				
Complication		x				
Adverse event		x	x	x	x	x
Postoperative outcomes			x	x	x	x

Additional File

Additional file 1 SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents.

Figures

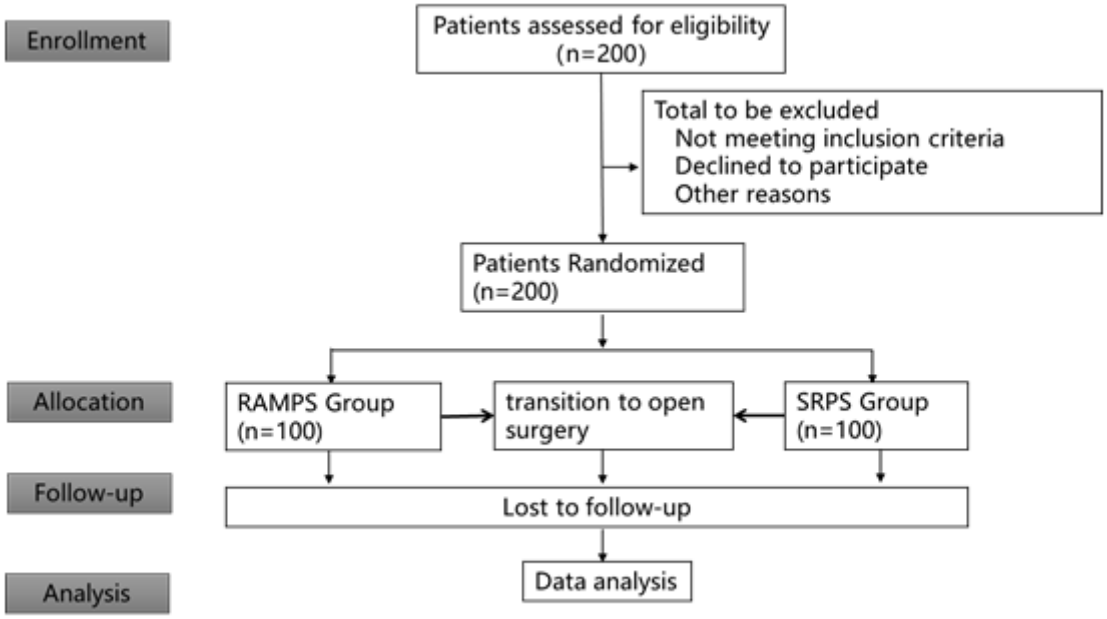

Figure 1

Consolidated Standards of Reporting Trials (CONSORT) flow diagram

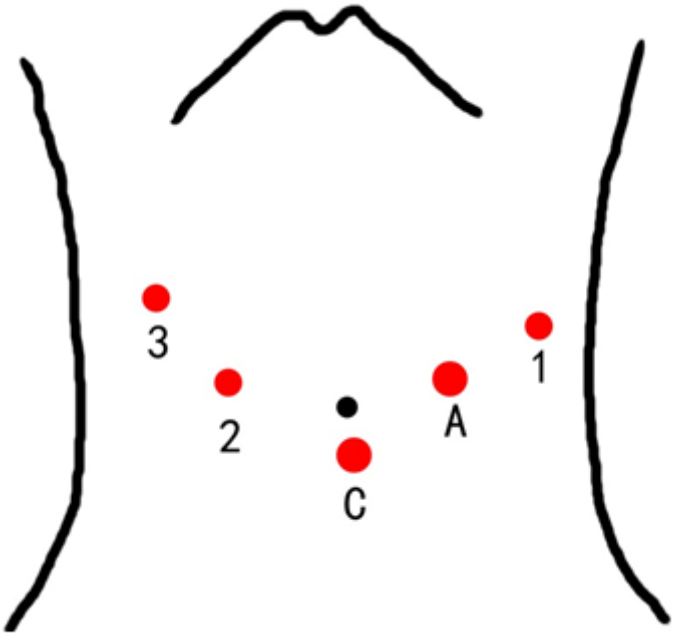

Figure 2

Robotic port placement for RDP. C, 12-mm trocar for camera; A, 12-mm trocar for assistant instruments; 1, 8-mm trocar for right robotic arm; 2, 8-mm trocar for left robotic arm; 3, 8-mm trocar for the fourth robotic arm

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- 2013SPIRIT.pdf