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

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.

Background

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 radical anterograde modular pancreaticosplenectomy (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. Compared with SRPS, RAMPS showed significant improvement in R0 resection rate and 5-year survival rate**[5, 6]**

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**[7-10]**. 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 abdominal surgery in the future**[11]**.

However, previous studies on RAMPS were conducted under laparotomy and laparoscopy, and there is still a lack of clinical studies on the safety and clinical efficacy of robotic radical anterograde modular pancreatectomy (RAMPS) in the world. Therefore, we need an RCT to compare short-term surgical oncological outcomes between Robotic RAMPS and SRPS for patients with distal pancreatectomy.

Methods

Study Aim

The aim of our study is to compare the safety and prognosis with robotic radical anterograde modular pancreaticosplenectomy (RAMPS) and standard retrograde pancreatosplenectomy (SRPS) in the treatment of pancreatic body and tail cancer.

Study Setting

A single-center, randomized, phase III study. The study protocol adheres to the SPIRIT statement (Additional file 1).

Endpoints

The primary efficacy endpoint of the trial will be the rates of margins and the number of lymph node retrieval. The second endpoints are: (1) 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 [12]; (2) perioperative indicators; such as operation time, blood loss, blood transfusion volume, transition rate to open surgery, postoperative hospitalization days, hospital costs.

Sample size

Determination of the postoperative 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%[13, 14]. 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% [15] . According to these studies, we used a two-sided log-rank test with 80% power at the 0.05 level of significance requires 123 patients in each group (NCSS and PASS 11 (NCSS Statistical Software, Kaysville, UT, USA)). Therefore, the total sample size required is n = 246 patients.

Inclusion criteria

1. The tumor was diagnosed as resectable by preoperative pathological examination or clinical judgment
2. It meets the indications of resection of pancreatic somatococcygeal carcinoma by robot;
3. Postoperative pathological diagnosis of pancreatic ductal adenocarcinoma;
4. Complete clinical data.

Exclusion criteria

1. Preoperative imaging examination or intraoperative exploration revealed distant metastasis and abandonment of surgery;
2. Preoperative chemotherapy or radiotherapy;
3. Patients with major complications who cannot tolerate surgery;
4. Complicated with or secondary other malignant tumors.

Participating surgeons

Differences in the surgical experience of surgeons may lead to differences in the incidence of complications. To prevent surgeon bias, our doctors have experience of more than 40 RDPs. Our surgical team consists of three doctors who are all skilled at using Da Vinci robotic systems for RAMPS and SRPS. In this research, 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.

Randomization

After confirmation of the eligibility criteria, including written informed consent, registration is made to the central registry in Chinese PLA General Hospital (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)

Data collection and statistics

All patients will be prospectively collected, including history, physical examination, laboratory data, pathological examination, perioperative clinical information, and complications. Data will be collected and stored securely through computer data sheets. All enrolled cases will be managed by randomly assigned CPGH codes. 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).

An independent research physician (SBP) 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.

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.

Concurrent and supportive treatments

Antibiotics, blood products, analgesics, H2 blockers and proton pump inhibitors will be determined by the surgeon for intraoperative and postoperative management. In addition, there are no regulations for drugs used to control complications and adverse events. Records are given for specific adverse events.

Discussion

In 1882, Trendelemburg completed the world's first tail resection of the pancreas[19]. 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 [20]. 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 [21]and has a better R0 resection rate than traditional tail pancreatectomy (70%-80%)[22]. 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 [15].

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

The trail will be started in August 2019. At the time of submission for this paper (June 2019), protocol version is ver.1.0. The approximate date when recruitment will be completed in September 2022. And the completion date is estimated to be December 2022.

Abbreviations

RAMPS	Radical antegrade modular pancreatosplenectomy
SRPS	Standard retrograde pancreatosplenectomy
RCT	Randomized controlled trial
OS	Overall survival
RFS	Relapse-free survival
CRF	Clinical report form
CPGH	Chinese PLA General Hospital

Declarations

Ethics approval and consent to participate

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

Not applicable.

Availability of data and material

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

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Authors’ contributions

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.

Competing interests

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

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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**	**POD 3**	**POD 7**	**POD 30**
Informed consent	x					
Personal data	x					
CT/MRI	x					
Blood tests	x		x	x	x	x
Trial intervention		x				
Intraoperative outcomes		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

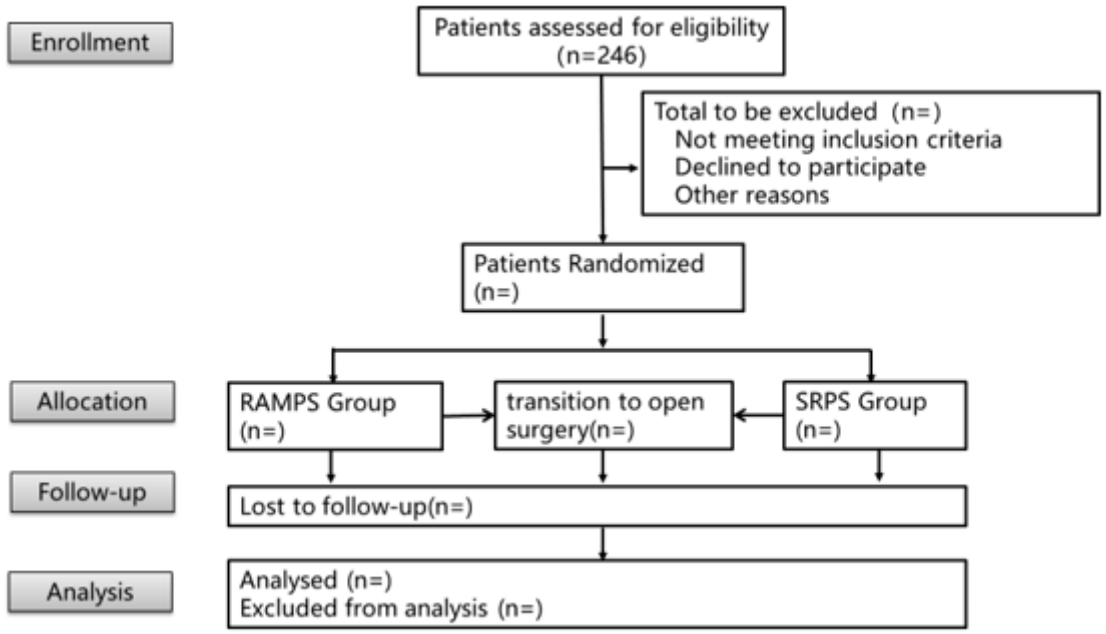

Figure 1

Consolidated Standards of Reporting Trials (CONSORT) flow diagram

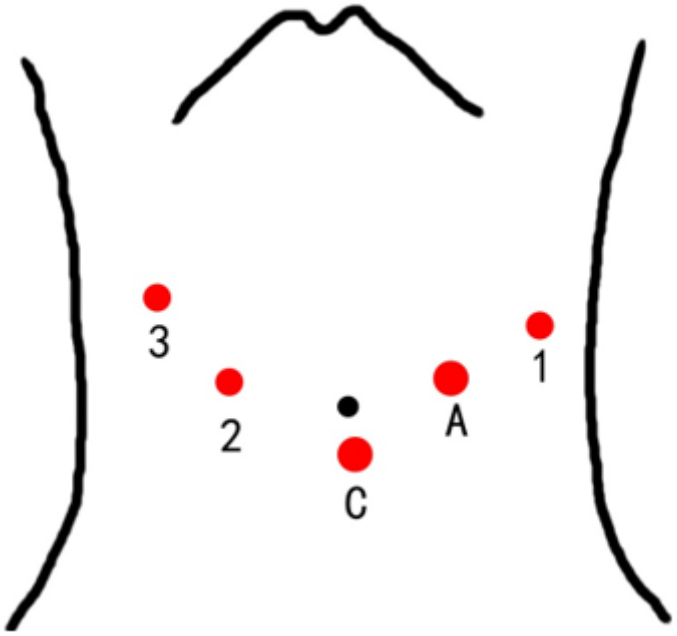

Figure 2

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.

- supplement1.pdf