

# Clinical Trial Protocol

## Title

A Prospective Non-randomized Controlled Multi-center Study of Laparoscopic Intracorporeal Distal Rectal Transection by Using the Traditional Approach vs. Using Transanterior Obturator Nerve Gateway Approach for Ultralow Rectal Cancers

## NCT No.

Not assigned yet

## Date

2021/9/7

## Principle Investigator Name

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## **Investigator Affiliation**

Peking University First Hospital

## **Co-ordinating Investigators**

Hekai Chen (Tianjin Fifth Central Hospital), Xiping Ding (Shengli Oilfield Hospital) and Qihong Wang (The Second Affiliated Hospital of Baotou Medical College).

## **Trial sites**

Multi-center

## **Methodology**

Prospective, Non-randomized, Interventional, Controlled

*The Biomedical Research Ethics Committee of Peking University First Hospital* is overseeing the research. (Phone: 010-66119025; Email: [bdyyl@126.com](mailto:bdyyl@126.com); Address: Xishiku Street No.8, Xicheng District, Beijing, 100034, People's Republic of China)

## **Background**

Since 1992 when intersphincteric resection (ISR) for rectal cancer was first proposed by Braun et al, ISR has been widely used since it can significantly improve patients' quality of life by preserving the anus, especially for those with low rectal cancer<sup>[1-4]</sup>. A series of studies have demonstrated its safety and feasibility. Standard laparoscopic ISR can not only ensure the radical resection of the tumor, but also preserve the anus<sup>[5-7]</sup>.

Laparoscopic ISR with double stapling technique (DST) can provide a clearer view of the narrow pelvic and intersphincteric space, and the minimally invasive approach can relieve postoperative pain, shorten hospital stay, and generate better cosmetic outcomes compared with traditional combined abdominal perineal resection<sup>[8]</sup>.

The wide application of ISR and DST has greatly improved the anal preservation rate for low rectal cancers, but the technical difficulty has also been obviously increased. In addition, for ultralow rectal cancers, because of the limited pelvic space, laparoscopic distal rectal transection could only be finished by multiple staplings resulting in an overlong stapling line, which could increase the risk for postoperative anastomotic leakage rate, which would seriously affect the patient's recovery and quality of life. Or the limited space could make it almost impossible to remove enough rectum to ensure a radical resection of the tumor, so distal rectal resection would have to be performed by converting to a transanal approach, that would definitely prolong the operative time and also increase the risk for anastomotic leakage. Although many scholars have tried to solve this problem<sup>[9-12]</sup>, all the methods have failed to fundamentally solve the problem of "the oblique dissection" of the distal rectum for ultralow rectal cancers.

To solve the problem above, on the basis of a large number of ISR-DST performing experience, Dr Tang, the director of this clinical trial has explored a new distal rectal resection method-- transanterior obturator nerve gateway approach. This approach can conspicuously expand the pelvic space and optimize the dissection angle without significantly prolonging the operative time, thus reducing the technical difficulty. So, by using this method, it would be more likely to preserve the anus and reduce the possibility of converting to transanal approach without breach of tumor's radical resection. The purpose of this clinical trial is to prospectively collect and compare data on the patients' perioperative items and postoperative functional and oncological outcomes of this novel approach with the traditional approach, so as to confirm the safety and feasibility of this novel approach and its advantages over the traditional approach.

## References

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## Objective

To confirm the safety, feasibility and advantages by comparing the perioperative variables, postoperative functional and oncological outcomes of patients with ultralow rectal cancer treated by laparoscopic traditional distal rectal dissection vs. by transanterior obturator nerve gateway approach.

## Patients

Patients with ultralow ( $\leq 5$ cm from the anal verge) rectal cancer who are to undergo laparoscopic radical resection (ISR- DST) without any contraindications of general anesthesia, surgery or chemotherapy.

### ➤ Inclusion criteria

- 1) Age: 18-80 years old;
- 2) Pathologically diagnosed as rectal cancer with the lower margin of the tumor from the anal margin  $\leq 5$ cm;
- 3) CT, MRI or endoscopic ultrasonography: Single tumor, clinical T stage  $\leq 3$  or no invasion of the internal sphincter, maximum diameter  $\leq 10$ cm, no distant metastasis;
- 4) The patient or the patient-authorized representative completely understands the study protocol and voluntarily participates in this study, agrees to sign written informed consent.

### ➤ Exclusion criteria

- 1) The patient had previous abdominal surgery that will significantly infect the laparoscopic procedures;
- 2) Patients requiring emergency surgery owing to intestinal obstruction, perforation, or uncontrolled bleeding caused by tumor;
- 3) Patients with poor anal function preoperatively (Wexner score  $\geq 10$ );
- 4) ASA (American Society of Anesthesiologists) grading  $\geq IV$ ;
- 5) Pregnant patients;
- 6) Patients concomitant with severe mental illness;
- 7) The patient or the patient-authorized representative can't understand the contents and objectives of the study.

➤ **Withdraw criteria**

- 1) ISR cannot be performed by intraoperative evaluation and is replaced by Miles surgery;
- 2) Distant metastasis is confirmed intraoperatively or by postoperative pathological findings;
- 3) Patients had other primary tumors requiring surgical/drug treatment during the study, or had other illnesses that prevent the patient from continuing to participate this study;
- 4) Patients decide to withdraw from the study for any reason, or who are unable to complete the study because of any objective reasons.

### **Sample size**

Two groups are designed, patients who are to receive the traditional approach to transect the distal rectum are assigned to the control group, patients who are to receive the transanterior obturator nerve gateway approach to transect the distal rectum are assigned to the experimental group. 100 cases are to be enrolled for the experimental group and not less than 100 cases are to be enrolled for the controlled group.

### **Treatment**

If the participant matches with the requirements for this study and agrees to take part in it, once hospitalized, the participant will complete the established preoperative tests including blood routine, the comprehensive metabolic panel, blood coagulation function, tumor markers, blood type, infectious disease screening tests, chest, abdominal and pelvic CT (Computed Tomography) scan and MRI, colonoscopy, echocardiogram, pulmonary function, venous duplex ultrasound of legs. All male patients will be routinely asked to fill

in the IIEF-5 sexual function scoring questionnaire preoperatively.

The following comprehensive treatment will be depended on the examination results:

➤ **Neoadjuvant therapy**

The treatment plan will be made in accordance with the NCCN (National Comprehensive Cancer Network) Guidelines for Diagnosis and Treatment of Colorectal Cancer (Version 1.2021).

Neoadjuvant chemoradiotherapy: Pelvis radiotherapy with a total dose of 50 Gy with 25 courses in 5 weeks. Neoadjuvant chemotherapy include single drug therapy: capecitabine (CAP, 1250 mg/m<sup>2</sup>, BID) or double drug therapy: oxaliplatin combined with capecitabine (CapeOX, oxaliplatin 130 mg/m<sup>2</sup>, day 1, capecitabine 1000mg/ m<sup>2</sup>, day 1 ~ 14, then rest for 7 days, repeated every 3 weeks) or three-drug therapy (mFOLFOX6, oxaliplatin 85 mg/ m<sup>2</sup> intravenous infusion for 2 hours, leucovorin calcium 400 mg/m<sup>2</sup> intravenous infusion for 2 hours, 5-FU (fluorouracil) 400 mg/m<sup>2</sup> intravenous infusion for 1 day, Then 1200 mg/ m<sup>2</sup>/d×2 days of continuous intravenous infusion with a total of 2400mg/m<sup>2</sup> for 46 ~ 48 hours, repeated every 2 weeks.

Abdominal and pelvic MRI and contrast enhanced CT will be routinely performed 6 to 8 weeks after neoadjuvant therapy to confirm the extent of tumor regression without new-found distant metastasis. Those whose clinical stage after neoadjuvant therapy changes from T4 to T3 will be seen as eligible in this study.

➤ **Surgical treatment**

● Preoperative preparation

- 1) Patients older than 60 years old or having a smoking history for over 10 years will receive lung ventilation training and atomization treatment for 3 days
- 2) Intestinal preparation will be done with oral cathartic medications 12-24 hours before surgery
- 3) Prophylactic antibiotics will be given once anesthesia is begun, the second antibiotics will be given if the operation lasts for over 3 hours
- 4) Urethral catheterization will be routinely done preoperatively
- 5) If the patient refuses to accept the novel approach before surgery, they will be directly enrolled in the traditional group. If both approaches are acceptable to the patient, the decision whether to use the novel approach will be made according to the intraoperative

conditions (see operating procedures below).

- Operating procedures

General anesthesia; Modified lithotomy position (Fig. 1a); Establishment of pneumoperitoneum: Place a trocar 1cm above the umbilicus through which to establish pneumoperitoneum and keep the abdominal pressure as 12 mmHg (millimeters of mercury).

Trocar placement: above the umbilicus (trocar C, 10 mm), upper right and left quadrants (trocars B and D, 5 mm), lower right quadrant (trocar A, 12 mm), lower left quadrant (trocar E, 5 mm), the midpoint between the pubic symphysis and umbilicus (trocar F, 5 mm).

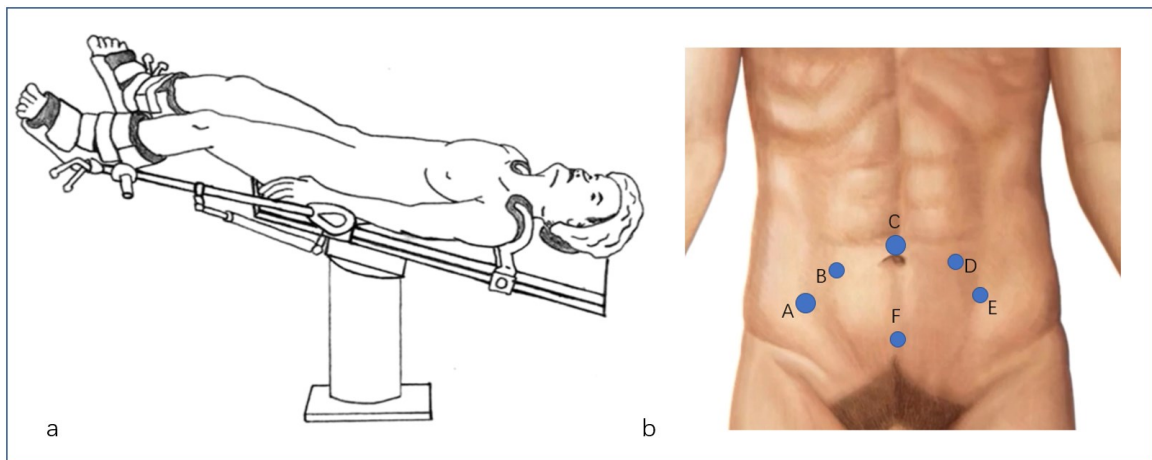


Fig.1 Patient position and trocar placement

Abdominal exploration: Explore the abdominal cavity in accordance with the principle of non-contact, from far to near step by step, explore the tumor finally.

The mesosigmoid and mesorectum are dissected from the right lateral rectum towards the root of the inferior mesenteric artery (IMA). The IMA is transected and ligated, so is the inferior mesenteric vein. Posterior space of the descending colon is dissected following opening the peritoneum beside the left rectum. The rectum in the pelvis is mobilized from posterior rectal space, anterior rectal space to bilateral rectal space successively. The lower edge of the tumor is marked by a clamp. The linear stapler is placed in the pelvis to clamp the distal rectum below the tumor to see if the transection can be done more than 1cm from the lower edge of the tumor. If yes, the distal rectum will be transected by the traditional approach (that means the patient will be assigned to the traditional group). The proximal bowel is transected through a small midline incision. Then the coloanal

anastomosis will be done intracorporeally. A surgical drain is placed in the pelvis and a terminal ileostomy is routinely performed. All incisions are closed.

If the distal rectal transection cannot be done more than 1cm from the lower edge of the tumor, the anterior obturator nerve gateway approach will be used (that means the patient will be assigned to the experimental group). The steps are as follows: The peritoneum covering the ureter and external iliac artery is opened more than 2 cm across the vas deferens (male) or round ligament (female). The Retzius space and vesicohypogastric fascia are exposed. The obturator vessels and obturator nerve are properly identified. Care should be taken to avoid any injury when using energy devices near the obturator nerve. The gateway is then opened through the TME (total mesorectal excision) compartment and the lateral compartment. If necessary, an “endoloop” can be placed through the gateway, and the bundled S2-4 nerves, ureter and bladder vessels are gently retracted toward the cranial direction to widen the gap. The linear stapler is placed in the gateway to vertically transect the distal rectum. The following procedures are the same with the traditional group as described above.

During the operation, the following variables will be recorded: the angle between the linear stapler and the rectum, distance from the lower edge to the resecting margin, whether the operation converted to transanal approach, operative time, bleeding volume, anastomotic height from anal verge and the length of the stapling line.

➤ **Postoperative management:**

The following information will be recorded:

1) Vital signs (body temperature, pulse rate, respiration rate, blood pressure) are routinely monitored, gross volume of fluid input and output will be recorded every 24h, blood routine, the comprehensive metabolic panel and coagulation function tests will be performed every 3 days.

2) The time of catheter removal (days after operation), residual urine volume in the bladder will be measured by ultrasound examination. Whether there is a request to be re-catheterized or take oral medication to relieve the dysuria. All patients will be asked to fulfil the IPSS (International prostate symptom score) questionnaire to assess urinary function.

**Table 1.** International prostate symptom score assessing urinary function

In the past month:	Not at All	Less than 1 in 5	Less than Half the	About Half the	More than Half	Almost Always
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		Times	Time	Time	the Time	
1. Incomplete Emptying How often have you had the sensation of not emptying your bladder?	0	1	2	3	4	5
2. Frequency How often have you had to urinate less than every two hours?	0	1	2	3	4	5
3. Intermittency How often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5
4. Urgency How often have you found it difficult to postpone urination?	0	1	2	3	4	5
5. Weak Stream How often have you had a weak urinary stream?	0	1	2	3	4	5
6. Straining How often have you had to strain to start urination?	0	1	2	3	4	5
	None	1 Time	2 Times	3 Times	4 Times	5 Times
7. Nocturia How many times did you typically get up at night to urinate?	0	1	2	3	4	5
<b>Total Score</b>						

Score: 1-7: Mild 8-19: Moderate 20-35: Severe

- 3) The time of pelvic drain removal (days after operation)
- 4) Whether complicated with anastomotic leakage, ileus and long-lasting (more than 5 days) pulmonary or abdominal infection
- 5) All information of the pathologic report.
- 6) Postoperative hospital stay (days)

➤ **Postoperative chemoradiotherapy**

Radiotherapy program is the same with the neoadjuvant therapy. Chemotherapy will be advised for patients with stage II cancer accompanied with the following high-risk factors: histologically poorly differentiated with normal mismatched repair or stable microsatellite (MSS), pT4 (pathological stage T 4), vascular/nerve invasion, preoperative intestinal obstruction or perforation, ≤ 12 lymph nodes retrieved and R1 resection. The chemotherapy program is the same with neoadjuvant chemotherapy. If mismatch repair defect (dMMR) or high-level microsatellite instability (MSI-H) is confirmed by pathology, chemotherapy

will not be advised. Patients with stage III cancer will routinely receive chemotherapy.

## Follow-up

1) Information on general medical history and physical examination will be collected every 3 months for 3 years

2) Blood tumor markers of CEA (carcinoembryonic antigen) and CA19-9 (carbohydrate antigen 19-9) will be tested every 3 months for 3 years

3) Abdominal and pelvic ultrasound and chest X-ray examinations will be carried out every 3 months for 3 years

4) Abdominal and pelvic MRI or contrast enhanced CT scan will be done every year for 3 years

5) Colonoscopy will be performed within 1 year after surgery. If there is any abnormality, reexamination will be required within half a year. If no abnormality is found, once a year for 3 years. All new-found adenomas by the colonoscopy during follow-up are recommended to be resected.

6) Sexual function score is assessed by filling in the questionnaire (IIEF-5) both preoperatively and 1 year later since operation.

**Table 2.** International Index of Erectile Function-5 assessing sexual function

Over the past 6 months:					
1. How do you rate your confidence that you could get and keep an erection?	Very low 1	Low 2	Moderate 3	High 4	Very high 5
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration?	Almost never/never 1	A few times (much less than half the time) 2	Sometimes (about half the time) 3	Most times (much more than half the time) 4	Almost always/always 5
3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	Almost never/never 1	A few times (much less than half the time) 2	Sometimes (about half the time) 3	Most times (much more than half the time) 4	Almost always/always 5
4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	Extremely difficult 1	Very difficult 2	Difficult 3	Slightly difficult 4	Not difficult 5

5. When you attempted sexual intercourse, how often was it satisfactory for you?	Almost never/never 1	A few times (much less than half the time) 2	Sometimes (about half the time) 3	Most times (much more than half the time) 4	Almost always/always 5
IIEF-5 scoring:					

The IIEF-5 score is the sum of the ordinal responses to the 5 items.

22-25: No erectile dysfunction

17-21: Mild erectile dysfunction

12-16: Mild to moderate erectile dysfunction

8-11: Moderate erectile dysfunction

5-7: Severe erectile dysfunction

7) 3-year tumor-free survival (month): The time from operation to confirmation of tumor's local recurrence or distant metastasis. The end point of the patient lost to follow-up is the date of loss. 30 days is defined as one month

8) 3-year overall survival (month): The time from operation to death. The end point of the patient lost to follow-up is the date of loss. 30 days is defined as one month

9) Stoma closure time (months since operation). Anal function is assessed by Wexner scale 3 months and 12 months after stoma closure, respectively.

**Table 3.** Wexner score assessing anal function

Type of Incontinence	Frequency				
	Never	Rarely	Sometimes	Usually	Always
Solid	0	1	2	3	4
Liquid	0	1	2	3	4
Gas	0	1	2	3	4
Wear Pad	0	1	2	3	4
Lifestyle altered	0	1	2	3	4

Never - 0

Rarely - Less than once a month

Sometimes - Less than once a week or once a month

Usually - Once a day or once a week

Always - Once a day or more

Score: 0 Perfect; 20 Complete Incontinence

(As to possible risks and benefits of participating in this trial, see details in the *informed consent document*.)

**Study start date (actual)**

2020-12-01

### **Study completion date (anticipated)**

2025-12-01 (All outcomes of the last patient are recorded 3 years postoperatively, death or loss to follow-up of the last patient.)

### **Primary outcomes**

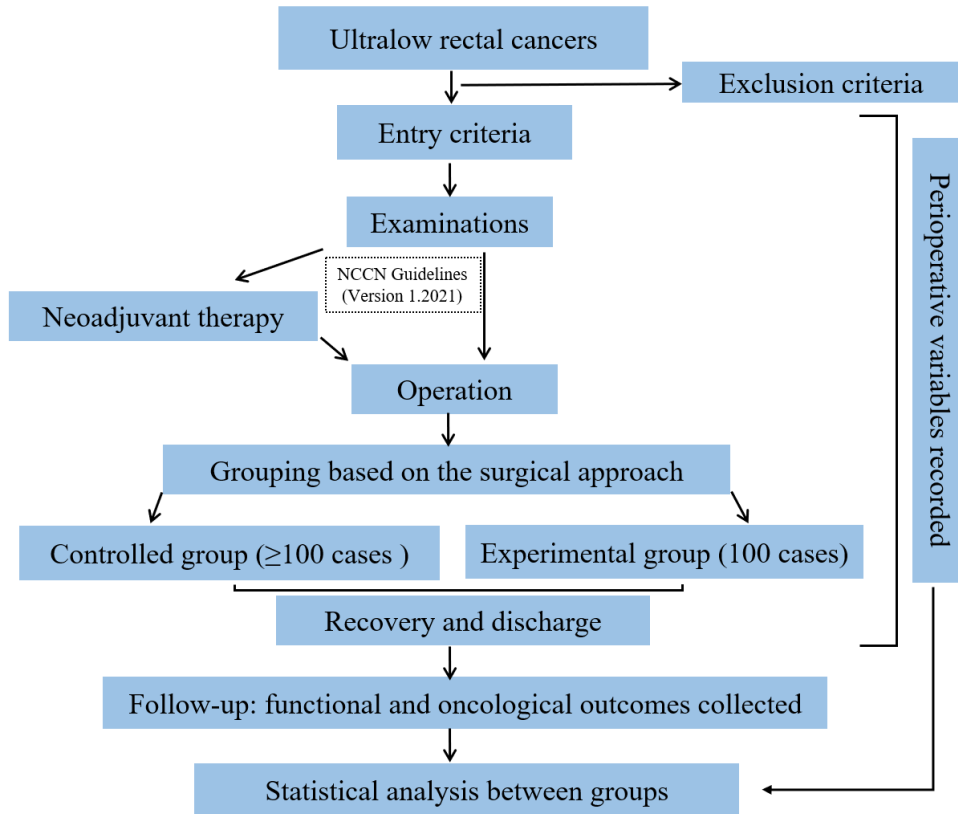
- The degree of Angle denotes the degree of angle between the linear stapler and the longitudinal axis of the rectum when transecting the distal rectum.
- The degree of  $\Delta$ Angle represents the degree of angle between the simulated stapling line with the total mesorectal excision approach and the real stapling line with the transanterior obturator nerve gateway approach (this outcome is measured only in patients of the experimental group).
- Length of distal resection margin indicates the shortest distance between the distal border of the tumor and the edge of the distal resection.
- Rate of conversion to transanal transection and anastomosis of the rectum: For each case, whether there is a conversion to transanal transection and anastomosis of the rectum during the operation will be recorded. The gross conversion rate (No. of cases undergoing conversion/total No. of cases enrolled \*100%) for each group will be calculated immediately after the last patient's surgery.
- Rate of anastomotic leakage: Whether the patient complicates with anastomotic leakage postoperatively will be followed up till 6 months after surgery. The gross anastomotic leakage rate (No. of cases diagnosed with anastomotic leakage/total No. of cases enrolled \*100%) for each group will be calculated 6 months after the last patient's surgery. Anastomotic leakage will be diagnosed if the patient has clinically apparent leakage signs (such as the emission of gas, pus, or feces from the pelvic drain, or peritonitis) or extravasation of endoluminally administered watersoluble contrast medium according to CT.

### **Statistics**

IBM SPSS (Statistical Package for the Social Sciences) Statistics 25 (IBM, Inc., Armonk, NY) will be used to perform statistical analyses. The *t* test and Mann-Whitney *U* test were used for quantitative data between groups. Qualitative data were compared by  $\chi^2$  or

Fisher's exact test and survival distributions were analyzed by log-rank test.

### Flow chart of the study



### Fund

This study is supported by Wu Jieping's Foundation Special for Clinical Research (320.6750.2021-04-2).

## **Informed Consent Document**

For the study:

*A Prospective Non-randomized Controlled Multi-center Study of Laparoscopic Intracorporeal Distal Rectal Transection by Using the Traditional Approach vs. Using Transanterior Obturator Nerve Gateway Approach for Ultralow Rectal Cancers*

**NCT No.**

Not assigned yet

## Date

2021/9/7

This study is being conducted by Dr. Jianqiang Tang, MD and associate professor at Department of General Surgery, Peking University First Hospital. Other researchers include Dr. Hekai Chen (Tianjin Fifth Central Hospital), Dr. Xiping Ding (Shengli Oilfield Hospital) and Dr. Qihong Wang (The Second Affiliated Hospital of Baotou Medical College). The Biomedical Research Ethics Committee of Peking University First Hospital is overseeing the research.

Please read this form carefully – it tells you about your rights in this study. Ask questions if you want more information about the form or the study.

If you decide to participate in this study you will sign this form – make sure you understand it completely before signing. We will give you a copy of this form to keep – it has important information like whom to contact if you have questions later.

➤ **What is this study about?**

Since 1992 when intersphincteric resection (ISR) for rectal cancer was first proposed by Braun et al, ISR has been widely used since it can significantly improve patients' quality of life by preserving the anus, especially for those with low rectal cancer. A series of studies have demonstrated its safety and feasibility. Standard laparoscopic ISR can not only ensure the radical resection of the tumor, but also preserve the anus. Laparoscopic ISR with double stapling technique (DST) can provide a clearer view of the narrow pelvic and intersphincteric space, and the minimally invasive approach can relieve postoperative pain, shorten hospital stay, and generate better cosmetic outcomes compared with traditional combined abdominal perineal resection. The wide application of ISR and DST has greatly improved the anal preservation rate for low rectal cancers, but the technical difficulty has also been obviously increased. In addition, for ultralow rectal cancers, because of the limited pelvic space, laparoscopic distal rectal transection could only be finished by multiple staplings resulting in an overlong stapling line, which could increase the risk for postoperative anastomotic leakage rate, which would seriously affect the patient's recovery and quality of life. Or the limited space could make it almost impossible to remove enough rectum to ensure a radical resection of the tumor, so distal rectal resection would have to be performed by converting to a transanal approach, that would definitely prolong the operative time and also increase the risk for anastomotic leakage. Although many scholars have tried to solve this problem, all the methods have failed to fundamentally solve the problem of "the oblique dissection" of the distal rectum for ultralow rectal cancers.

To solve the problem above, on the basis of a large number of ISR-DST performing experience, Dr Tang, the director of this clinical trial has explored a new distal rectal resection method-- transanterior obturator nerve gateway approach. This approach can conspicuously expand the pelvic space and optimize the dissection angle without significantly prolonging the operative time, thus reducing the technical difficulty. So, by using this method, it would be more likely to preserve the anus and reduce the possibility of converting to transanal approach without breach of tumor's radical resection. The purpose of this clinical trial is to prospectively collect and compare data on the patients' perioperative items and postoperative functional and oncological outcomes of this novel approach with the traditional approach, so as to confirm the safety and feasibility of this



novel approach and its advantages over the traditional approach.

### ➤ **Who are we asking to participate?**

Patients with ultralow rectal cancer ( $\leq 5$ cm from the anal verge) who are to undergo laparoscopic radical resection of rectal cancer (ISR-DST) without any contraindications of general anesthesia, operation or chemotherapy.

### **Inclusion criteria**

- 1) Age: 18-80 years old;
- 2) Pathologically diagnosed as rectal cancer with the lower margin of the tumor from the anal margin  $\leq 5$ cm;
- 3) CT (Computed Tomography), MRI (Magnetic Resonance Imaging) or endoscopic ultrasonography: Single tumor, clinical T stage  $\leq 3$  or no invasion of the internal sphincter, maximum diameter  $\leq 10$ cm, no distant metastasis;
- 4) The patient or the patient-authorized representative completely understands the study protocol and voluntarily participates in this study, agrees to sign written informed consent.

### **Exclusion criteria**

- 1) The patient had previous abdominal surgery that will significantly infect the laparoscopic procedures;
- 2) Patients requiring emergency surgery owing to intestinal obstruction, perforation, or uncontrolled bleeding caused by tumor;
- 3) Patients with poor anal function preoperatively (Wexner score  $\geq 10$ );
- 4) ASA grading  $\geq IV$ ;
- 5) Pregnant patients;
- 6) Patients concomitant with severe mental illness;
- 7) The patient or the patient-authorized representative can't understand the contents and objectives of the study.

### **Withdraw criteria**

- 1) ISR cannot be performed by intraoperative evaluation and is replaced by Miles surgery;
- 2) Distant metastasis is confirmed intraoperatively or by postoperative pathological findings;

- 3) Patients had other primary tumors requiring surgical/drug treatment during the study, or had other illnesses that prevent the patient from continuing to participate in this study;
- 4) Patients decide to withdraw from the study for any reason, or who are unable to complete the study because of any objective reasons.

➤ **What will you be asked to do?**

If you match with the requirements for this study and agree to take part in it, once hospitalized, you will complete the established preoperative tests including blood routine, the comprehensive metabolic panel, blood coagulation function, tumor markers, blood type, infectious disease screening tests, chest, abdominal and pelvic CT scan and MRI, colonoscopy, echocardiogram, pulmonary function, venous duplex ultrasound of legs. All male patients will be routinely asked to fill in the IIEF-5 (International Index of Erectile Function-5) sexual function scoring questionnaire preoperatively.

The following comprehensive treatment will be depended on the examination results:

**Neoadjuvant therapy**

The treatment plan will be made in accordance with the NCCN (National Comprehensive Cancer Network) Guidelines for Diagnosis and Treatment of Colorectal Cancer (Version 1.2021).

Neoadjuvant chemoradiotherapy: Pelvis radiotherapy with a total dose of 50 Gy with 25 courses in 5 weeks. Neoadjuvant chemotherapy include single drug therapy: capecitabine (CAP, 1250 mg/m<sup>2</sup>, BID) or double drug therapy: oxaliplatin combined with capecitabine (CapeOX, oxaliplatin 130 mg/m<sup>2</sup>, day 1, capecitabine 1000mg/ m<sup>2</sup>, day 1 ~ 14, then rest for 7 days, repeated every 3 weeks) or three-drug therapy (mFOLFOX6, oxaliplatin 85 mg/ m<sup>2</sup> intravenous infusion for 2 hours, leucovorin calcium 400 mg/m<sup>2</sup> intravenous infusion for 2 hours, 5-FU (fluorouracil) 400 mg/m<sup>2</sup> intravenous infusion for 1 day, Then 1200 mg/ m<sup>2</sup>/d×2 days of continuous intravenous infusion with a total of 2400mg/m<sup>2</sup> for 46 ~ 48 hours, repeated every 2 weeks.

Abdominal and pelvic MRI and contrast enhanced CT will be routinely performed 6 to 8 weeks after neoadjuvant therapy to confirm the extent of tumor regression without new-found distant metastasis. Those whose clinical stage after neoadjuvant therapy changes from T4 to T3 will be seen as eligible in this study.

## Surgical treatment

### Preoperative preparation

- 1) Patients older than 60 years old or having a smoking history for over 10 years will receive lung ventilation training and atomization treatment for 3 days
- 2) Intestinal preparation will be done with oral cathartic medications 12-24 hours before surgery
- 3) Prophylactic antibiotics will be given once anesthesia is begun, the second antibiotics will be given if the operation lasts for over 3 hours
- 4) Urethral catheterization will be routinely done preoperatively
- 5) If the patient refuses to accept the novel approach before surgery, they will be directly enrolled in the traditional group. If both approaches are acceptable to the patient, the decision whether to use the novel approach will be made according to the intraoperative conditions (see operating procedures below).

### Operating procedures

General anesthesia; Modified lithotomy position (Fig. 1a); Establishment of pneumoperitoneum: Place a trocar 1cm above the umbilicus through which to establish pneumoperitoneum and keep the abdominal pressure as 12mmHg (millimeters of mercury).

Trocar placement (Fig. 1b): above the umbilicus (trocar C, 10 mm), upper right and left quadrants (trocars B and D, 5 mm), lower right quadrant (trocar A, 12 mm), lower left quadrant (trocar E, 5 mm), the midpoint between the pubic symphysis and umbilicus (trocar F, 5 mm).

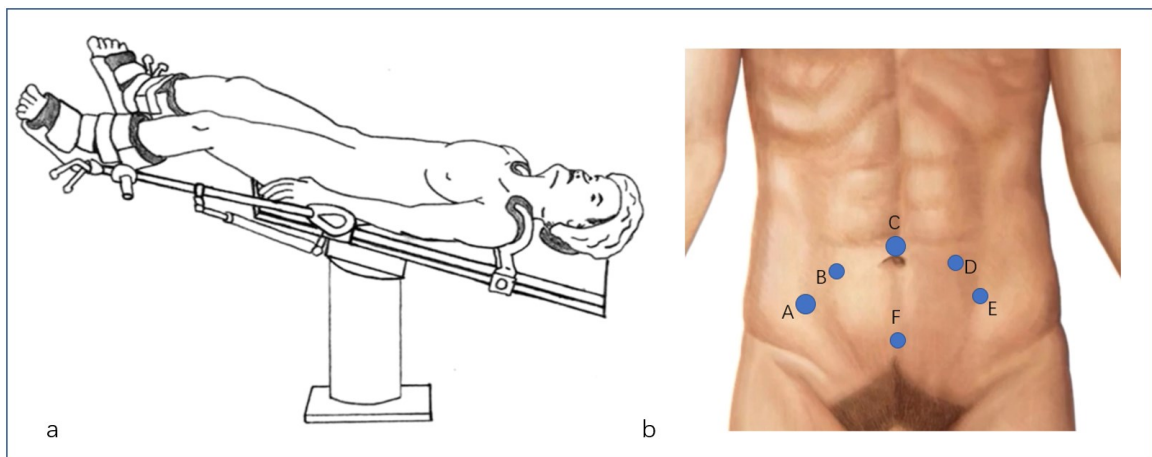


Fig.1 Patient position and trocar placement

Abdominal exploration: Explore the abdominal cavity in accordance with the principle of non-contact, from far to near step by step, explore the tumor finally.

The mesosigmoid and mesorectum are dissected from the right lateral rectum towards the root of the inferior mesenteric artery (IMA). The IMA is transected and ligated, so is the inferior mesenteric vein. Posterior space of the descending colon is dissected following opening the peritoneum beside the left rectum. The rectum in the pelvis is been mobilized from posterior rectal space, anterior rectal space to bilateral rectal space successively. The lower edge of the tumor is marked by a clamp. The linear stapler is placed in the pelvis to clamp the distal rectum below the tumor to see if the transection can be done more than 1cm from the lower edge of the tumor. If yes, the distal rectum will be transected by the traditional approach (that means the patient will be assigned to the traditional group). The proximal bowel is transected through a small midline incision. Then the coloanal anastomosis will be done intracorporeally. A surgical drain is placed in the pelvis and a terminal ileostomy is routinely performed. All incisions are closed.

If the distal rectal transection cannot be done more than 1cm from the lower edge of the tumor, the anterior obturator nerve gateway approach will be used (that means the patient will be assigned to the experimental group). The steps are as follows: The peritoneum covering the ureter and external iliac artery is opened more than 2 cm across the vas deferens (male) or round ligament (female). The Retzius space and vesicohypogastric fascia are exposed. The obturator vessels and obturator nerve are properly identified. Care should be taken to avoid any injury when using energy devices near the obturator nerve. The gateway is then opened through the TME (total mesorectal excision) compartment and the lateral compartment. If necessary, an “endoloop” can be placed through the gateway, and the bundled S2-4 nerves, ureter and bladder vessels are gently retracted toward the cranial direction to widen the gap. The linear stapler is placed in the gateway to vertically transect the distal rectum. The following procedures are the same with the traditional group as described above.

During the operation, the following variables will be recorded: the angle between the linear stapler and the rectum, distance from the lower edge to the resecting margin, whether the operation converted to transanal approach, operative time, bleeding volume,

anastomotic height from anal verge and the length of the stapling line.

## Postoperative management

The following information will be recorded:

1 ) Vital signs (body temperature, pulse rate, respiration rate, blood pressure) are routinely monitored, gross volume of fluid input and output will be recorded every 24h, blood routine, the comprehensive metabolic panel and coagulation function tests will be performed every 3 days.

2 ) The time of catheter removal (days after operation), residual urine volume in the bladder will be measured by ultrasound examination. Whether there is a request to be re-catheterized or take oral medication to relieve the dysuria. All patients will be asked to fulfil the IPSS (International prostate symptom score) questionnaire to assess urinary function.

**Table 1.** International prostate symptom score assessing urinary function

In the past month:	Not at All	Less than 1 in 5 Times	Less than Half the Time	About Half the Time	More than Half the Time	Almost Always
1. Incomplete Emptying How often have you had the sensation of not emptying your bladder?	0	1	2	3	4	5
2. Frequency How often have you had to urinate less than every two hours?	0	1	2	3	4	5
3. Intermittency How often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5
4. Urgency How often have you found it difficult to postpone urination?	0	1	2	3	4	5
5. Weak Stream How often have you had a weak urinary stream?	0	1	2	3	4	5
6. Straining How often have you had to strain to start urination?	0	1	2	3	4	5
	None	1 Time	2 Times	3 Times	4 Times	5 Times
7. Nocturia How many times did you typically get up at night to urinate?	0	1	2	3	4	5
<b>Total Score</b>						

Score: 1-7: Mild 8-19: Moderate 20-35: Severe

- 3) The time of pelvic drain removal (days after operation)
- 4) Whether complicated with anastomotic leakage, ileus and long-lasting (more than 5 days) pulmonary or abdominal infection
- 5) All information of the pathologic report.
- 6) Postoperative hospital stay (days)

### **Postoperative chemoradiotherapy**

Radiotherapy program is the same with the neoadjuvant therapy. Chemotherapy will be advised for patients with stage II cancer accompanied with the following high-risk factors: histologically poorly differentiated with normal mismatched repair or stable microsatellite (MSS), pT4 (pathological stage T 4), vascular/nerve invasion, preoperative intestinal obstruction or perforation,  $\leq 12$  lymph nodes retrieved and R1 resection. The chemotherapy program is the same with neoadjuvant chemotherapy. If mismatch repair defect (dMMR) or high-level microsatellite instability (MSI-H) is confirmed by pathology, chemotherapy will not be advised. Patients with stage III cancer will routinely receive chemotherapy.

### **Follow-up**

- 1) Information on general medical history and physical examination will be collected every 3 months for 3 years
- 2) Blood tumor markers of CEA (carcinoembryonic antigen) and CA19-9 (carbohydrate antigen 19-9) will be tested every 3 months for 3 years  
Abdominal and pelvic ultrasound and chest X-ray examinations will be carried out every 3 months for 3 years
- 3) Abdominal and pelvic MRI or contrast enhanced CT scan will be done every year for 3 years
- 4) Colonoscopy will be performed within 1 year after surgery. If there is any abnormality, reexamination will be required within half a year. If no abnormality is found, once a year for 3 years. All new-found adenomas by the colonoscopy during follow-up are recommended to be resected.
- 5) Sexual function score is assessed by filling in the questionnaire (IIEF-5) both

preoperatively and 1 year later since operation.

**Table 2. International Index of Erectile Function-5 assessing sexual function**

Over the past 6 months:					
1. How do you rate your confidence that you could get and keep an erection?	Very low 1	Low 2	Moderate 3	High 4	Very high 5
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration?	Almost never/never 1	A few times (much less than half the time) 2	Sometimes (about half the time) 3	Most times (much more than half the time) 4	Almost always/always 5
3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	Almost never/never 1	A few times (much less than half the time) 2	Sometimes (about half the time) 3	Most times (much more than half the time) 4	Almost always/always 5
4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	Extremely difficult 1	Very difficult 2	Difficult 3	Slightly difficult 4	Not difficult 5
5. When you attempted sexual intercourse, how often was it satisfactory for you?	Almost never/never 1	A few times (much less than half the time) 2	Sometimes (about half the time) 3	Most times (much more than half the time) 4	Almost always/always 5
IIEF-5 scoring:					

The IIEF-5 score is the sum of the ordinal responses to the 5 items.

22-25: No erectile dysfunction

17-21: Mild erectile dysfunction

12-16: Mild to moderate erectile dysfunction

8-11: Moderate erectile dysfunction

5-7: Severe erectile dysfunction

6) 3-year tumor-free survival (month): The time from operation to confirmation of tumor's local recurrence or distant metastasis. The end point of the patient lost to follow-up is the date of loss. 30 days is defined as one month

7) 3-year overall survival (month): The time from operation to death. The end point of the patient lost to follow-up is the date of loss. 30 days is defined as one month

8) Stoma closure time (months since operation). Anal function is assessed by Wexner

scale 3 months and 12 months after stoma closure, respectively.

**Table 3.** Wexner score assessing anal function

Type of Incontinence	Frequency				
	Never	Rarely	Sometimes	Usually	Always
Solid	0	1	2	3	4
Liquid	0	1	2	3	4
Gas	0	1	2	3	4
Wear Pad	0	1	2	3	4
Lifestyle altered	0	1	2	3	4

Never - 0

Rarely - Less than once a month

Sometimes - Less than once a week or once a month

Usually - Once a day or once a week

Always - Once a day or more

Score: 0 Perfect; 20 Complete Incontinence

➤ **Are there any possible risks to you?**

No matter which group you are assigned into, the treatment program will be in accordance with the NCCN guideline, except that the transection of the distal rectum is performed by the transanterior obturator nerve gateway approach for patients in the experimental group. As this is a novel approach, the long-term affection both on the functional and survival outcomes are not clear yet. There are possibly both advantages and disadvantages by using this novel approach. Possible disadvantages might include:

- 1) When constructing transanterior obturator nerve gateway, the obturator nerve and vessels might be damaged resulting in numbness and paraesthesia on the medial aspect of the thigh and weakness in adduction of the thigh and intraoperative bleeding.
- 2) As the construction of transanterior obturator nerve gateway will anyhow destroy the normal local anatomical structure of the pelvis, if the tumor relapses in the pelvis postoperatively, the technical difficulty of the second operation might be increased.

➤ **Will you benefit from participation?**

As stated above, there are possibly both advantages and disadvantages by using this novel



approach. Possible advantages might include:

- 1) Although it will take some time (about 5 minutes) to construct the transanterior obturator nerve gateway, the novel approach can also obviously enlarge the pelvic space, that will lower the difficulty of the following procedures, thus, the total operative time for patients in the experimental group might be shorter.
- 2) With a more satisfactory transecting angle, the novel approach can be more likely to obtain long-enough distal resection margin, that will help to lower the rate of conversion to transanal approach.
- 3) With a more satisfactory transecting angle, less stapler firings will be taken to perform the distal rectal transection, that will not only reduce the risk for anastomotic leakage, but also reduce the hospitalization costs.
- 4) With a more satisfactory transecting angle, it will be more likely to preserve the anus.

➤ **Will it cost you anything to participate?**

Just the time it takes to complete the questionnaire and the follow-up.

➤ **Will you receive anything for participating in the study?**

No.

➤ **How will your information be kept private?**

Confidentiality will be provided to the fullest extent possible by law. We will not share any information that we collect that can identify you unless we legally have to. Any information that could identify you will be deleted. Your answers will be stored in a database protected by a password.

➤ **What if you don't want to participate or change your mind partway through?**

Participating in this study is completely voluntary. You can refuse to participate or quit at any time, for any reason. Your decision to stop participating will not influence the relationship you may have with the researchers or study staff or the nature of your

relationship with the hospital you are in, or in the future. In the event you withdraw from the study, all associated data collected will be immediately destroyed wherever possible.

➤ **Who can you call if you have more questions?**

If you have any questions about the research or your participation in the study, feel free to contact Dr. Jianqiang Tang at 010-66119025 or [doc\\_tjq@hotmail.com](mailto:doc_tjq@hotmail.com)

This research is approved by the Biomedical Research Ethics Committee of Peking University First Hospital that oversees the ethics of research at Peking University First Hospital. If you have any questions about your rights – or if you have concerns about the study – you may contact them at 010-66119025 or [bdyyl@126.com](mailto:bdyyl@126.com).

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## Subject Consent

I have read this consent form completely. I have been encouraged to ask questions, and have received helpful answers. I understand that:

- My participation is voluntary
- I may quit at any time without penalty

I do  I do not give you permission to record me during this study.

I do  I do not give you permission to share my information – with no identifying information – with other researchers for future studies.

I voluntarily agree to participate in this study.

Participant's Signature \_\_\_\_\_ Date \_

\_\_\_\_\_

Investigator's Signature \_\_\_\_\_ Date \_

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