Statistical analysis plan (SAP)

Effect of intermittent urethral catheter clamping combined with active urination training (ICCAUT) strategy on postoperative urinary dysfunction after radical rectal cancer surgery: Statistical analysis plan for the single-center randomized controlled trial (ICCAUT -1)

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LIST OF ABBREVIATIONS

ICCAUT	interITTent catheter clamping combined with active urination training
CRBD	Catheter-Related Bladder Discomfort
ICIQ-SF	International Consultation on Incontinence Questionnaire-Short Form
ITT	Modified intention-to-treat
PP	Per-protocol
CI	Confidence intervals
IPSS	International Prostate Symptom Score
APR	abdominoperineal resection
cRC	Clinical Research Coordinator
PPA	per-protocol analysis set
ATA	as-treated analysis set
OR	odds ratios
SAP	statistical analysis plan
FD	free-drainage
LAR	low anterior resectio
RUV	residual urine volume
LOCF	Last Observation Carried Forward
ISR	intersphincteric resection
TCA	Turnbull-Cutait Pull-Through Coloanal Anastomosis
TaTME	total mesorectal excision
ARD	absolute risk differences
CRM	Circumferential Resection Margin
pCR	pathological complete response
DRM	Distal Resection Margin

1 Introduction

The ICCAUT trial is a single - center, prospective, two - arm, parallel - group randomized controlled study. It aims to investigate the effect of the intermittent catheter clamping combined with active urination training (ICCAUT strategy) on urinary retention and secondary catheterization after proctectomy. The aims, hypotheses, and design of the ICCAUT trial are detailed in the protocol. This statistical analysis plan (SAP) focuses on the upcoming analysis and presentation of the trial data. This SAP is based on the study protocol version 2.0. The comprehensive study design, including primary and secondary endpoints, methods for determining sample size, and the approach to data management, are essential parts of the SAP. They are crucial for understanding the trial's methodology and result interpretation.

We develop this statistical analysis plan before completing the enrollment. This helps avoid issues like selection bias in analysis methods and multiple comparisons. These issues could occur if the plan is not determined in advance.

2 Study description

2.1 Study design

The ICCAUT trial is a single - center, prospective, two - arm, parallel - group randomized controlled study. It compares intermittent catheter clamping combined with active urination training to free draining of the urinary catheter. The aim is to investigate the effect of the intermittent catheter clamping combined with active urination training (ICCAUT strategy) on urinary retention and secondary catheterization after proctectomy. Recruitment began on March 20, 2024. Patients are being recruited from the Department of Gastrocolorectal Surgery, General Surgery Center of the First Hospital of Jilin University in Changchun, Jilin Province, China. Study participants are rectal cancer patients who need low anterior resection (LAR) or abdominoperineal resection (APR). This trial was designed to enroll 400 patients by February 2026. As of the formatting of this SAP, 362 cases have been enrolled.

The trial was prospectively registered on clinicaltrial.gov (NCT06241703). The initial trial version was version 1.1.1. A minor revision was made and published in version 1.1.2 (1). Study protocol version 2.0 was updated, mainly focusing on measures to control the dropout rate and reduce bias. This SAP version 1.0 is developed based on study protocol version 2.0 and focuses on the analysis and presentation of trial data.

2.2 Treatment allocation

Patients who meet the inclusion criteria will be randomly assigned to the ICCAUT group or the free-drainage (FD) group. Stratified randomization will be performed based on the following two factors: (1) sex and (2) whether APR was performed. The allocation ratio of the ICCAUT and FD group will be 1:1.

3 Objective

3.1 Primary

The primary objective of this study is to investigate the impact of the ICCAUT strategy on urinary dysfunction in patients undergoing laparoscopic or robot - assisted proctectomy.

3.2 Secondary

The secondary objective of this study is to investigate whether the ICCAUT strategy is associated with an increased risk of postoperative urinary tract infection.

4 Endpoints

4.1 Primary Endpoint

The primary endpoint of this study is a composite endpoint. For the sake of convenience, we define this composite endpoint as urinary dysfunction in this study. It consists of incomplete bladder emptying after the first voiding following catheter removal or the need for secondary catheterization.

Incomplete bladder emptying is defined as a post-void residual urine volume (RUV) in the bladder greater than 100 ml (2–6). The method to measure RUV is detailed in the study protocol (1).

The criteria for determining the need for secondary catheterization are also detailed in the study protocol (1). Patients who undergo re-catheterization for reasons other than urinary retention will also be recorded as positive primary endpoint events. However, a sensitivity analysis will be conducted on these patients. The specific analysis method is described in the section “6.5.2.2 Sensitivity analysis for positive primary endpoints caused by reasons other than urinary retention”.

4.2 Secondary endpoints

The secondary endpoints of this study are as follows: 1) the incidence of urinary tract infections associated with the catheter, 2) the time to first void after catheter removal, 3) CRBD grade, 4) evaluation of voiding function after catheter removal using the ICIQ-SF and International Prostate Symptom Score (IPSS), 5) Evaluation of the incidence, type, and grade of complications within 30 days postoperatively, and 6) Incidence rate of residual urine volume greater than 200 ml after the first voiding.

5 Sample size

The sample size is calculated based on a differential test, with urinary dysfunction as the primary endpoint. Based on our preliminary research results, the incidence of urinary dysfunction in the bladder training group is 44.7%, and in the direct removal group, it is 59.3%. Patients are randomly assigned to the two groups in a 1:1 ratio. With a one-sided significance level α of 0.05 and a power (1-β) of 80%, the sample size was calculated using PASS 15 software. Each group, the bladder training group and the direct removal group, requires 180 cases. Assuming a dropout rate of 10%, each group requires 200 cases. Therefore, this trial needs a total of 400 cases.

6 Statistical methods

6.1 General calculation rules

All statistical tests were 2-sided, and statistical significance was set at $P < 0.05$. All statistical analyses were performed using R or SPSS. P-values will be quoted to three decimal places. Confidence intervals (CI) will be two-sided and 95% CI will be quoted to one decimal place.

Categorical variables will be reported as frequencies and percentages. Percentages will be quoted to one decimal place. Chi-square tests in contingency tables will be replaced by Fisher's exact tests if any expected cell frequency is less than five. Absolute risk differences and the corresponding 95% CI will be calculated.

Continuous data with normal distribution were presented as mean (standard deviation) and analyzed by Student's t-test. Continuous variables with non-normal distribution were reported as medians (quartile) and compared using the Mann–Whitney U test. Hodges-Lehmann method will be used to calculate the difference in median and the corresponding 95% CI. Data will be quoted to one decimal place.

6.2 Analysis populations

6.2.1 Full analysis set

The comparison analysis of the primary outcome will be conducted on the basis of the "Intent-to-Treat (ITT)" analysis. The ITT analysis will include all the randomized patients and group the patients according to their randomization. In the ITT analysis, patients randomized to the ICCAUT group will be analyzed as part of the ICCAUT group. This is true even if they didn't receive any bladder training and had the catheter removed directly. Similarly, patients randomized to the Free - drainage group will be analyzed as members of the Free - drainage group, even if they ultimately received bladder training. The study needs to record the specific reasons for not following the planned procedure.

6.2.2 Per-protocol analysis set

In the per-protocol analysis set (PPA), only cases that strictly follow the randomization and the assigned treatment plan will be included in the analysis. Patients who do not receive treatment according to the assigned randomization plan

will be excluded from the PPA. The excluded patients include: 1) Patients who did not have their urinary catheters removed on the second day after surgery for various reasons, with the catheter removal time being either advanced or postponed; 2) Patients who did not carry out bladder training strictly according to the plan; 3) Patients who had to use selective α1 adrenergic receptor blockers due to their medical conditions during their first catheterization.

6.2.3 As-treated analysis set

In the as-treated analysis set (ATA), we will analyze patients based on the actual treatment they received, rather than the treatment assigned by randomization. The ATA analysis set will include all the patients in the ITT analysis set. However, in terms of grouping, in the ATA analysis, patients who receive at least one round of bladder training are classified as the bladder training group, while those who do not receive training are classified as the direct removal group.

6.3 Missing data and its handling approaches

6.3.1 Definition of Missing Data

Since the primary endpoint is a composite endpoint, if a patient fails to achieve any of the positive events within the primary endpoint (secondary catheterization or residual urine volume > 100 ml) and any of the following situations occurs: 1) the residual urine volume after the first urination following the removal of the urinary catheter is missing; or 2) the situation of secondary catheterization within 7 days after the removal of the urinary catheter is missing, the primary endpoint will be defined as missing. The possible reasons for the missing primary endpoint include: 1) loss to follow - up or death, making it impossible to know whether secondary catheterization occurs within 7 days after the removal of the urinary catheter; 2) after the removal of the urinary catheter, due to various reasons, the bladder ultrasound for assessing the residual urine volume after the first urination is not carried out in a timely manner; 3) the patient refuses the researcher to use the data related to the patient's own micturition function.

In the case where a subject refuses the researcher to use their personal data, that

is, the subject requests to withdraw the informed consent and drop out of this study midway, all the data of this patient will be treated as missing data in the ITT analysis. If the subject refuses the collection of research data after withdrawal but consents to the collection of data before withdrawal, the researcher will treat the data after withdrawal as missing values, and the data before withdrawal can be included in the analysis.

6.3.2 Methods for handling missing data

In this study, if the missing rate of the primary endpoint is less than 5%, no imputation of missing data will be done in the analysis of the primary endpoint in the ITT, PPA, and ATA sets. During the analysis of the primary outcome, missing data will be treated as censored.

If the missing rate of the primary endpoint is 5% or higher at the end of the study, the following procedures will be adopted to handle the data with missing values in any variable of the primary endpoint.

1) When the data on post-void residual urine volume (RUV) by ultrasound after the first urination is complete, and the situation of secondary catheterization within 7 days after the removal of the urinary catheter is also complete. There is no missing data.

2) When the data on post-void RUV by ultrasound after the first urination is complete, but the situation of secondary catheterization within 7 days after the removal of the urinary catheter is missing.

If the post-void RUV by ultrasound after the first urination is greater than 100 ml, handling method: The primary endpoint is reached (positive), and no imputation of missing data for secondary catheterization is performed.

If the post-void RUV by ultrasound after the first urination is less than or equal to 100 ml, handling method: Multiple imputation method is used to impute the missing data of secondary catheterization.

3) When the data on post-void RUV by ultrasound after the first urination is missing, but the situation of secondary catheterization within 7 days after the removal of the urinary catheter is complete.

If secondary catheterization occurs within 7 days after the removal of the urinary catheter, handling method: The primary endpoint is reached (positive), and no imputation of missing data for RUV is performed.

If secondary catheterization does not occur within 7 days after the removal of the urinary catheter, and the post-void RUV by ultrasound after the second urination is not missing, handling method: The Last Observation Carried Forward (LOCF) method is used to impute the missing data of the first residual urine volume. In LOCF method, the post-void RUV after the second urination is used to impute missing data of the first post-void RUV.

If secondary catheterization does not occur within 7 days after the removal of the urinary catheter, and the post-void RUV by ultrasound after the second urination is also missing, handling method: Multiple imputation method is used to impute the missing data of the first post-void RUV.

4) When the data on post-void RUV by ultrasound after the first urination is missing, and the situation of secondary catheterization within 7 days after the removal of the urinary catheter is also missing.

If the post-void RUV by ultrasound after the second urination is not missing, handling method: The LOCF method is used to impute the missing data of the first residual urine volume. If the imputed residual urine volume is greater than 100 ml, the primary endpoint is reached (positive), and no imputation of missing data for secondary catheterization is performed; if the imputed residual urine volume is less than or equal to 100 ml, multiple imputation method is used to impute the missing data of secondary catheterization.

If the post-void RUV by ultrasound after the second urination is also missing,

handling method: Multiple imputation method is used to impute the missing data of the primary endpoint. At this time, the primary endpoint is imputed as a whole missing data, rather than imputing the RUV and secondary catheterization separately.

Through the above treatment methods, we will minimize the impact of missing data on the research results and ensure the accuracy and reliability of data analysis. The handling process of missing data in primary endpoint is shown in Figure 1.

In the analysis of secondary endpoint and subgroup analysis, we will not perform imputation of missing data.

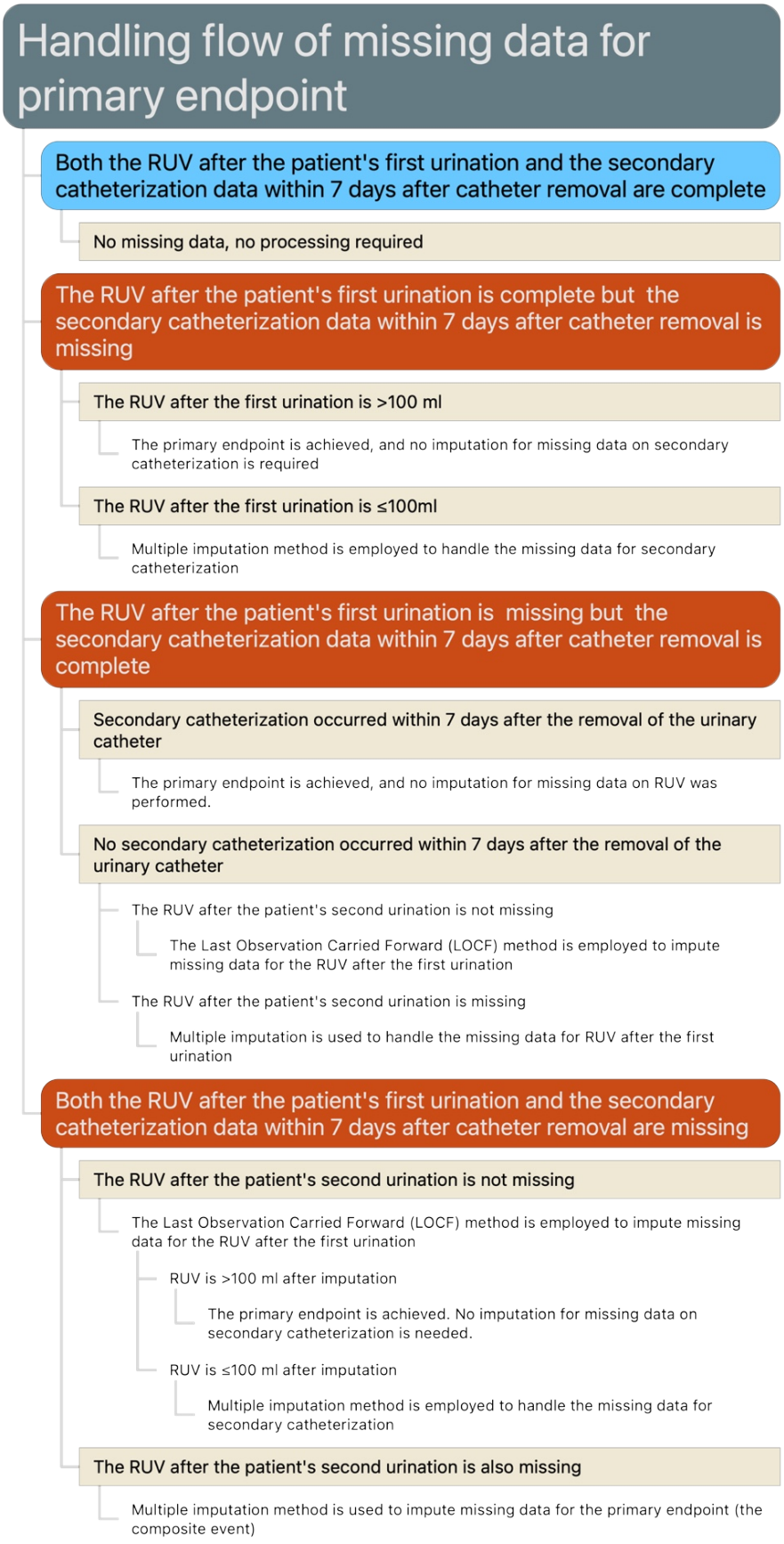

Figure 1 Imputation Scheme for Missing Data of the Primary Endpoint

6.4 Characteristics of the population

The following baseline characteristics will be presented in ITT, Per-protocol（PP）and as-treated (AT) population.

6.4.1 Preoperative characteristics

- Sex, categorical variable: male, female;
- Age, continuous variable, measured in years;
- Body Mass Index, continuous variable, measured in kg/m^2;
- American Society of Anesthesiologists grading, categorical variable: I, II, III, IV;
- Neoadjuvant radiotherapy/chemoradiotherapy, categorical variable: no, yes;
- Tumor site, categorical variable: the lower edge of the tumor is above the peritoneal reflection, the lower edge of the tumor is not above (below or at) the peritoneal reflection.
- The distance from the lower edge of the tumor to the anal margin, continuous variable, measured in centimeter;
- Benign prostatic hyperplasia, categorical variable: No, Yes;
- History of hypertension, categorical variable: No, Yes;
- History of diabetes, categorical variable: No, Yes;
- ICIQ-SF score at admission, continuous variable, measured in points;
- ICIQ-SF classification at admission, categorical variable: no or mild, moderate, severe;
- IPSS score at admission, continuous variable, measured in points;
- IPSS classification at admission, categorical variable: mild, moderate, severe;
- Clinical T stage, categorical variable: clinical complete response (cCR), T1, T2, T3, T4;
- Clinical N stage, categorical variable: N0, N1, N2;
- Clinical TNM stage, categorical variable: 0 stage, I stage, II stage, III stage, IV stage.

6.4.2 Operative characteristics

- Surgical techniques, categorical variable: laparoscopic-assisted surgery, robotic-

assisted surgery;

- Surgical procedure, categorical variable: low anterior resection (LAR), abdominoperineal resection (APR). Subtypes of LAR include LAR with prophylactic enterostomy, LAR with intersphincteric resection (ISR), LAR with Turnbull-Cutait Pull-Through Coloanal Anastomosis (TCA), LAR with transanal total mesorectal excision (TaTME). There is overlap among different subtypes of LAR.
- Operation time, continuous variable, measured in minutes;
- Anastomosis, categorical variable: no anastomosis, colorectal anastomosis, coloanal anastomosis;
- Intraoperative blood loss volume, continuous variable, measured in milliliters;
- Intraoperative urine output volume, continuous variable, measured in milliliters;
- Intraoperative intravenous infusion volume, continuous variable, measured in milliliters;

6.5 Analysis of endpoints

6.5.1 Analysis of the primary endpoint

Categorical variables will be statistically analyzed and described using counts (percentages). Without multivariate adjustment, the primary endpoints of the two groups will be compared respectively in the ITT analysis set, the PPA set, and the ATA set. The differences between the two groups will be described using the absolute risk differences (ARD) and their 95% Confidence Intervals (95% CI). The 95% CI will be compared with an absolute risk difference of 0.

The positive primary endpoint consists of bladder residual urine volume (RUV) >100ml after the first voiding or secondary catheterization within 7 days after the catheter removal. These two subtypes will also be compared between the two groups and their 95% confidence interval will be presented. Also, secondary catheterization for reasons other than urinary retention will be listed in the subsets of secondary catheterization.

Primary endpoint:

Dataset: ITT, PPA and ATA				
Variables	Free-drainage group N=***	ICCAUT group N=***	Absolute risk difference (95% CI)	P value
Urinary dysfunction	** (**)	** (**)	** (** to **)	*.***
RUV >100ml	** (**)	** (**)	** (** to **)	-
Secondary catheterization	** (**)	** (**)	** (** to **)	-
Urinary retention	** (**)	** (**)	** (** to **)	-
Not urinary retention (notes on the specific reasons)	** (**)	** (**)	** (** to **)	-
Missing data	** (**)	** (**)		

In addition, in the PPA set, the Chi-square test or Fisher's exact test will be used to analyze the variables related to the primary endpoint. Multivariate logistic regression will be employed to adjust the factors that may have an impact on the primary endpoint, and to analyze the independent risk factors affecting the primary endpoint. During this process, continuous variables will be transformed into categorical variables. The variables used for adjustment include the patient grouping in the PPA dataset (ICCAUT group/free-drainage group), tumor site (the lower edge of the tumor is above the peritoneal reflection/the lower edge of the tumor is below the peritoneal reflection), sex (male/female), and age (≤ 65 years old/ > 65 years old). In addition to the above variables, variables with a p-value < 0.1 in the univariate analysis will also be included. After adjustment, the differences between the groups will be described using the Odds Ratio (OR) and 95% CI.

Univariate analysis:

Dataset: PPA

Variables	Without Urinary dysfunction N=***	With Urinary dysfunction N=***	P value
Interventions			*.***
Free drainage	**(**)	**(**)	
ICCAUT	**(**)	**(**)	
Sex			*.***
Male	**(**)	**(**)	
Female	**(**)	**(**)	
Age			*.***
≤ 65 years old	**(**)	**(**)	
> 65 years old	**(**)	**(**)	
BMI			*.***
<24 kg/m^2	**(**)	**(**)	
≥24 kg/m^2	**(**)	**(**)	
ASA			*.***
I-II	**(**)	**(**)	
III-IV	**(**)	**(**)	
Neoadjuvant radiotherapy or chemoradiotherapy			*.***
No	**(**)	**(**)	
Yes	**(**)	**(**)	
Tumor site			*.***
Above the peritoneal reflection	**(**)	**(**)	
Below or at the peritoneal reflection	**(**)	**(**)	
Distance from the anal verge to the tumor			*.***
≤5 cm	**(**)	**(**)	
>5 cm	**(**)	**(**)	
Benign prostatic hyperplasia			*.***
No	**(**)	**(**)	
Yes	**(**)	**(**)	
IPSS classification at admission			*.***
Mild	**(**)	**(**)	
Moderate	**(**)	**(**)	
Severe	**(**)	**(**)	
ICIQ-SF classification at admission			*.***
No or mild	**(**)	**(**)	
Moderate	**(**)	**(**)	

Severe	**(**)	**(**)	
History of hypertension			*.***
No	**(**)	**(**)	
Yes	**(**)	**(**)	
History of Diabetes			*.***
No	**(**)	**(**)	
Yes	**(**)	**(**)	
Pathological stage T			*.***
pCR to T2	**(**)	**(**)	
T3 to T4	**(**)	**(**)	
Pathological stage N			*.***
N0	**(**)	**(**)	
N1 to N2	**(**)	**(**)	
Pathological stage TNM			*.***
0 to II	**(**)	**(**)	
III to IV	**(**)	**(**)	
Surgical techniques			*.***
Laparoscopic-assisted surgery	**(**)	**(**)	
Robotic-assisted surgery	**(**)	**(**)	
Surgical procedure			*.***
LAR	**(**)	**(**)	
APR	**(**)	**(**)	
Operation time			*.***
≤180 minutes	**(**)	**(**)	
>180 minutes	**(**)	**(**)	
Anastomosis			*.***
No anastomosis	**(**)	**(**)	
Colorectal anastomosis	**(**)	**(**)	
Coloanal anastomosis	**(**)	**(**)	
Intraoperative urine output volume			*.***
≤500 ml	**(**)	**(**)	
>500 ml	**(**)	**(**)	
Intraoperative intravenous infusion volume			*.***
≤1500 ml	**(**)	**(**)	
>1500 ml	**(**)	**(**)	
Duration of the indwelling urethral catheter			*.***

≤2 days	**(**)	**(**)	
>2 days	**(**)	**(**)	
Urinary tract infections			*.***
No	**(**)	**(**)	
Yes	**(**)	**(**)	

Multivariate analysis:

Dataset: PPA				
Variables	Without Urinary dysfunction N=***	With Urinary dysfunction N=***	Adjusted OR (95% CI)	P value
Interventions				*.***
Free drainage	**(**)	**(**)		
ICCAUT	**(**)	**(**)	** (** to **)	
Sex				*.***
Male	**(**)	**(**)	** (** to **)	
Female	**(**)	**(**)		
Age				*.***
≤ 65 years old	**(**)	**(**)		
> 65 years old	**(**)	**(**)	** (** to **)	
Tumor site				*.***
Above the peritoneal reflection	**(**)	**(**)		
Below or at the peritoneal reflection	**(**)	**(**)	** (** to **)	
Other variables with p value <0.1 in univariate analysis	**(**)	**(**)	** (** to **)	*.***

6.5.2 Sensitivity analysis of primary endpoints.

This study will conduct sensitivity analyses on the missing data of the primary endpoints and positive events of the primary endpoints caused by reasons other than urinary retention. The sensitivity analyses of the two situations above will be conducted in the ITT analysis set.

6.5.2.1 Sensitivity analysis of missing data

If the missing rate of the primary endpoint is < 5%, no imputation of the primary

endpoint will be done in the ITT analysis set. If the missing rate of the final primary endpoint is ≥ 5%, data imputation will be carried out according to the imputation scheme for missing primary endpoint data in Figure 1 in the ITT analysis set.

For the sensitivity analysis in both of the above situations, all missing primary endpoints will be imputed as positive events or all as negative events. Then, the analysis of these two extreme cases will be performed in the ITT population.

6.5.2.2 Sensitivity analysis for positive primary endpoints caused by reasons other than urinary retention

In this study, some patients may have secondary catheterization for reasons other than urinary retention. These events can include:

1) Patients ask for secondary catheterization because of urgent urination or a strong fullness feeling, but the urine volume drained after secondary catheterization is no more than 100 ml.

2) Patients need secondary catheterization due to situations like unplanned secondary surgery, urethral injury, shock, consciousness disorder, intestinal obstruction, bleeding, transfer to ICU, etc.

In such cases, we still record it as a positive primary endpoint, but will conduct a sensitivity analysis for these cases.

For these patients:

1. If there is data on the bladder residual urine volume after the first urination and it is > 100 ml, it is still regarded as a positive primary endpoint, and no sensitivity analysis is done.

2. If there is no data on the bladder residual urine volume after the first urination or it is ≤ 100 ml, then a sensitivity analysis is needed. In the sensitivity analysis, these patients will be treated as negative events for the primary endpoint.

Sensitivity analysis of primary endpoint:

Dataset: ITT

Variables	Free-drainage group N=***	ICCAUT group N=***	Absolute risk difference (95% CI)	P value
Urinary dysfunction: all missing primary endpoints are imputed as positive events	** (**)	** (**)	** (** to **)	*.***
Urinary dysfunction: all missing primary endpoints are imputed as negative events	** (**)	** (**)	** (** to **)	*.***
Urinary dysfunction: Cases resulting from reasons other than urinary retention are defined as negative primary endpoints, and all missing primary endpoints are imputed as positive events	** (**)	** (**)	** (** to **)	*.***
Urinary dysfunction: Cases resulting from reasons other than urinary retention are defined as negative primary endpoints, and all missing primary endpoints are imputed as negative events	** (**)	** (**)	** (** to **)	*.***

6.5.3 Analysis of secondary endpoints

In the analysis of secondary endpoints, continuous variables will be described using the mean ± standard deviation or the median (interquartile range); categorical variables will be described using counts (percentages). Missing values for secondary endpoints will neither be imputed nor subjected to sensitivity analysis.

Secondary endpoints:

Variables	Type	Effect size	P value
Urinary tract infection	categorical variable: no, yes	Absolute risk difference (95% CI)	*.***
The time from catheter removal to the first micturition	continuous variable: hours	Difference (95% CI) by Hodges-Lehmann method	*.***
Catheter-related bladder discomfort (CRBD)	categorical variable: level 0, level 1, level 2, level 3	Absolute risk difference (95% CI)	*.***
ICIQ-SF score on the second day after the first removal of the urinary catheter	continuous variable: points	Difference (95% CI) by Hodges-Lehmann method	*.***

ICIQ-SF classification on the second day after the first removal of the urinary catheter	categorical variable: no or mild, moderate, severe	Absolute risk difference (95% CI)	*.***
IPSS score on the second day after the first removal of the urinary catheter	continuous variable: points	Difference (95% CI) by Hodges-Lehmann method	*.***
IPSS classification on the second day after the first removal of the urinary catheter	categorical variable: mild, moderate, severe	Absolute risk difference (95% CI)	*.***
Surgical Complications within 30 days after surgery	categorical variable: no, yes	Absolute risk difference (95% CI)	*.***
Specific types of complications	categorical variable: no, yes	-	-
……	……	-	-
Clavien - Dindo Classification of Surgical Complications ≥III	categorical variable: no, yes	Absolute risk difference (95% CI)	*.***
Bladder residual urine volume > 200 ml after the first voiding	categorical variable: no, yes	Absolute risk difference (95% CI)	*.***

Other outcomes of interest：

- Self-assessment form on the quality of bladder training, presented in the form of a bar chart.
- Postoperative hospital stays, continuous variable, measures in days;
- Duration of urinary catheter indwelling, categorical variable: within 1 day, 2 days, ≥3 days;
- Time from catheter removal to second catheterization, categorical variable: within 1 day, 2 days, ≥3 days;
- Volume of first urination after surgery, continuous variable, measures in milliliters;
- Methods of second catheterization, categorical variable: indwelling urinary catheter, indwelling suprapubic puncture tube;
- Volume of urine drained by the second catheterization, continuous variable, measures in milliliters;
- Pathological outcomes, include:
  - Tumor volume, continuous variable, measures in cm^3;
  - Circumferential Resection Margin (CRM) distance, continuous variable, measures in millimeters;
  - Positive CRM rate, categorical variable: negative, positive;

- Distal Resection Margin (DRM) distance, continuous variable, measures in millimeters;
- Positive DRM rate, categorical variable: negative, positive;
- Pathological stage T, categorical variable: pathological complete response (pCR), Tis, T1, T2, T3, T4;
- Pathological stage N, categorical variable: N0, N1, N2;
- Pathological stage TNM, categorical variable: 0 stage, I stage, II stage, III stage, IV stage;
- Number of harvested lymph nodes, continuous variable, measures in piece;
- Number of metastatic lymph nodes, continuous variable, measures in piece.

6.5.4 Subgroup analysis

We will explore differences in the primary endpoint between the two groups in different subgroups through subgroup analysis. Logistic regression will be used for univariate and multivariate analyses, with effect sizes represented by OR and 95% CI, and interaction P-values will be calculated. The subgroups include:

- Sex: male, female
- Age: ≤65 years, >65 years
- Tumor site: the lower edge of the tumor is above the peritoneal reflection; the lower edge of the tumor is below or at the peritoneal reflection
- Other variables independently associated with primary endpoints in multivariate analysis.

6.6 Explorative analysis

We will conduct an exploratory analysis of urinary tract infections. The main focus is to explore the independent related factors affecting urinary tract infections after rectal surgery. The analysis methods include univariate analysis, multivariate analysis, and subgroup analysis.

7 Interim analyses

No interim analyses are planned in this study.

8 Timing of analysis

We will conduct the primary endpoint analysis of the study after all patients have completed their first postoperative month follow-up and will publish the relevant research findings. The results of the exploratory analysis will be published as a post hoc analysis after the publication of the primary outcomes.

9 References

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