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Feasibility and safety of hybrid transvaginal natural orifice transluminal endoscopic surgery for colon cancer: Protocol for a multicenter, single-arm, phase II trial (vNOTESCA)

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ABSTRACT

Introduction: It has been a decade since the first patient with colon cancer underwent colectomy by hybrid transvaginal natural orifice transluminal endoscopic surgery (hvNOTES). However, the efficacy and safety of this procedure is not well established.

Methods: This study is an open-label, multicenter, single-arm, phase 2 trial undertaken at six centers in China. Female patients aged over 18 years and below 80 years old with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, with pathologically proven, resectable, cT1-3N0-2M0 disease who have previously untreated colon cancer are eligible for inclusion. The primary endpoint is a composite of major intraoperative and postoperative complications (greater than grade III, the Common Terminology Criteria for Adverse Events [CTCAE], version 5.0). Secondary endpoints include conversion to laparoscopic or open surgery, postoperative concentration of C-Reactive Protein and procalcitonine, complete pathological assessment of complete mesocolic excision specimens, postoperative pain, amount of narcotic pain medication administered, time to first flatus after surgery, number of harvested lymph nodes, R0 resection rate, length of hospital stay, sexual function assessment, quality of recovery, satisfaction with surgical scars, quality of life, postoperative recurrence patterns, relapse-free survival, and overall survival.

Ethics and dissemination: The study was approved by the Research Ethics Committee, Renmin Hospital of Wuhan University, China, number: WDRY2022-K053. All patients will receive written information of the trial and provide informed consent before enrollment. The results of this trial will be disseminated in academic conferences and peer-reviewed medical journals.

Trial registration number NCT04048421.

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Strengths and limitations of this study

- To our knowledge, this is the first prospective clinical feasibility and safety study to evaluate hybrid transvaginal natural orifice transluminal endoscopic surgery for radical resection of colon cancer.
- A strength of this study is the careful monitoring of any major intraoperative or postoperative complications associated with the procedure.
- If the novel procedure for radical resection of colon cancer is proved to be safe, the oncological effectiveness of this procedure will subsequently be compared with the standard laparoscopic approach in a randomized controlled, phase III trial.
- Limitations of this study are the small sample size, absence of a control group, and the broad eligibility criteria for study population.
- Different postoperative systemic regimens are allowed, which might result in heterogeneity of clinical outcomes.

1. Introduction

Minimally invasive surgery (MIS) was developed with an effort to address morbidities associated with open surgery, such as tissue damage, postoperative pain, recovery time, and stress response, etc. [1,2] Thus far, it has brought to fruition the promises of less tissue damage [3], less pain [4], shortened recovery time [5–7], and lower adhesion-related readmissions [8], but postoperative pain, recovery time, burden of readmissions associated with adhesion, and other physiopsychological disturbances—while reduced—have not been eliminated [8], and efforts continue [9,10].

Natural orifice transluminal endoscopic surgery (NOTES) is a novel "incisionless" surgical technique with gaining entry through a natural body orifice (mouth, anus, vagina, or urethra) and then breaching the wall of the stomach, colon, rectum, posterior vaginal fornix, or bladder to enter the peritoneum or other body spaces and perform surgical procedures by using either a flexible endoscopy or a laparoscopy, which aims to reduce the impact of surgical incisions and is heralded as a paradigm shift in MIS [11]. Transvaginal NOTES (vNOTES) is the most popularly used technique, which offers advantages of a well-known entry site into the peritoneum through a posterior colpotomy, and the use of flexible endoscopic or traditional laparoscopic equipment and rigid instruments, [9,12] or more recently, robotic flexible or rigid instruments [13,14]. Hybrid vNOTES (hvNOTES) is an attempt to combine the advantages of vNOTES, while allowing the procedures to be easier by virtue of the small-sized abdominal trocars for countertraction, exposure, and triangulation [15,16].

Although several case reports and small case series have revealed that hvNOTES is safe and feasible for treatment of colon cancer [17–21], our current understanding of this novel procedure is still limited. The discrepancy between deep skepticism of public opinion and currently available data highlights the uncertainty that still exists in the paradigm of hvNOTES and will continue to be a barrier to its acceptance and future application [22]. Therefore, well-designed and well-conducted studies are needed to define its clinical applications.

To the knowledge of the authors, vNOTESCA is the first study that prospectively explores the feasibility, safety, utility, and efficacy

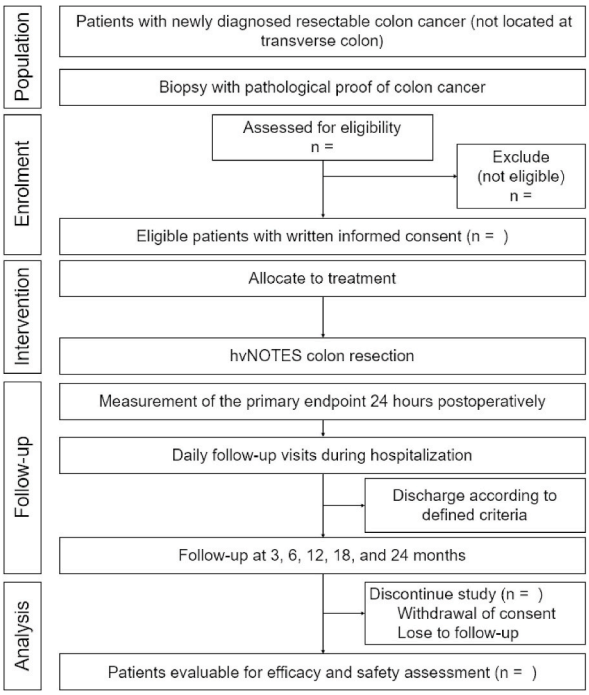

Fig. 1. Study flow chart. hvNOTES, hybrid transvaginal natural orifice transluminal endoscopic surgery.

of hvNOTES as a surgical treatment in female patients with colon cancer. This study will help gaining valuable insights into this gap in knowledge.

2. Methods and analysis

2.1. Trial design

The vNOTESCA trial is a prospective, open-label, multicenter, single-arm, phase II clinical trial performed by high-volume colorectal cancer centers in China. This trial was registered with ClinicalTrials.gov under registration number NCT04048421. The trial scheme is shown in Fig. 1.

2.2. Study population and eligibility criteria

All female patients aged over 18 years and below 80 years old with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, with pathologically proven, resectable, cT1-3N0-2M0 disease who have previously untreated colon cancer are eligible for inclusion (Table 1).

2.3. Trial locations

The vNOTESCA trial will be conducted at six high-volume colorectal cancer centers with expertise for hvNOTES in China:

1. Renmin Hospital of Wuhan University
2. Qingdao Municipal Hospital
3. Beijing Friendship Hospital of Capital Medical University
4. Daping Hospital of Army Medical University
5. The Second Affiliated Hospital of Zhejiang University
6. The Third Xiangya Hospital of Central South University

Table 1
Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
• Female.	•Patients who did not experience complete sexual intercourse before surgery.
• Age: 18 − 80 years old.	• Patients who previously underwent intestinal surgery with any cause.
• BMI <28 kg/m^2.	• cT4 tumor.
• American Society of Anesthesiologists score: class I to III.	• With complications of colon cancer including bleeding, obstruction, or perforation.
• Eastern Cooperative Oncology Group (ECOG) performance status: 0 or 1.	• Patients who previously received neoadjuvant chemo- or radiotherapy for colon cancer.
• Diagnosed colonic adenocarcinoma by endoscopy with biopsy-based tests.	• Patients who are diagnosed with other malignant tumors within 5 years.
• Tumor size ≤5 cm.	• Vulnerable patients.
• Involving one single colon segment:	• Vaginal stenosis.
a. Right colon, which is from the ileocecal valve up to and including the hepatic flexure.	• Prior vaginal reconstructive surgery, not including hysterectomy.
b. Left colon, which is from the splenic flexure to the junction between the sigmoid and descending colon.	• Myocardial infarction or unstable angina within the past 6 months.
c. Sigmoid colon, which is between the descending colon and the rectum (≥15 cm from the dentate).	• Cerebrovascular accident within the past 6 months.
• Clinical stage cT1 − T3, cN0 − N2.	• Continuous systemic steroid administration within 1 month before the surgery.
• No locally advanced disease that renders laparoscopic resection impossible.	• Patients who are participating or were enrolled in other clinical trial within 6 months.
• Not transverse colon cancer located between distal hepatic flexure and proximal splenic flexure.	• Pregnancy or breastfeeding.
• No evidence of distant metastasis in preoperative studies.	• History of pelvic radiation therapy.
• No synchronous colon cancers demonstrated by complete preoperative colonoscopy.	• An anticipated need for ostomy during operation.
• One of the following elective operations that may be safely performed by current techniques is required:	• Urgent or emergent surgery.
a. Right hemicolectomy	• Patients with prior or suspected inflammatory bowel disease (Crohn's disease or ulcerative colitis), or familial polyposis.
b. Left hemicolectomy	
c. Subtotal colectomy	
d. Sigmoid colectomy	
• Patients who agree with participating in the trial with informed consents and have the ability and willingness to comply with the requirements of the protocol including follow-up.	

2.4. Intervention

With the patient under general anesthesia, one 5 mm or 12 mm trocar is placed in the umbilicus and a 12–15 mmHg carbon dioxide pneumoperitoneum is achieved. Two additional 5 mm trocars are inserted in the right and/or left flanks where appropriate. A single-hole laparoscopic approach system is inserted into the abdominal cavity transvaginally through an about 3.0 cm posterior colpotomy. After exploration of the abdomen, standard splenic flexure or hepatic flexure mobilization is performed with an initial laparoscopic approach for left or right hemicolectomy. Then all procedures or most of them are performed transvaginally with conventional rigid laparoscopic instruments. The corresponding arteries and veins are divided at their origin. The mesocolon is mobilized and adequate lymph node harvesting is guaranteed. The small intestine, colon, and/or rectum are then divided with stapler to secure distal and proximal resection margins. The specimen is put into a retrieval bag and removed transvaginally. Intracorporeal side-to-side anastomosis or end-to-end anastomosis is performed as per the surgeon's standard of care. Drainage tubes may be used. The colpotomy is closed with resorbable thread transvaginally.

2.5. Surgical quality control

The participating hospitals are high-volume colorectal cancer centers with a caseload of at least 300 colectomies per year over the last 3 years. Only surgeons that are experienced to perform hvNOTES will be eligible to participate in this trial.

2.6. Perioperative management, discharge, and follow-up

Perioperative venous thromboembolism (VTE) prophylaxis will be performed according to the National Comprehensive Cancer Network (NCCN) guidelines [23]. Single-shot antibiotics will be administrated about 30 min before incision. Postoperatively, intravenous patient-controlled analgesia is administered for 24 h. Then, analgesics will be applied orally. Daily blood samples are scheduled on POD1, and 3. Diet progression is strictly controlled to allow accurate assessment of bowel function recovery. A sip of water is allowed after first flatus passage, and a soft diet is initiated when water being tolerated well. Other postoperative protocols follow each site's policy. Patients will be encouraged to discharge from POD 5 once completely meet the discharge criteria, including: more than POD 5, tolerable pain controlled with oral analgesics, ability to full oral diet, having at least one passage of stool, regular vaginal wound healing (no complains of vaginal bleeding, discharge, or dehiscence), and no evidence of infection-related complications. Patients with lymph node involvement (pN+) are offered 6 cycles of adjuvant chemotherapy, usually mFOLFOX6 regimen as per the discretion of the medical oncologist, within 4 weeks after surgery. Follow-up will be starting at the date of colectomy for 2 years. Specifically, every 4 weeks until 3 months, every 3 months until 6 months, every 6 months for 2 years. At each follow-up examination schedule, a complete history is taken, physical examination and routine tests are performed. Complete blood count, liver profile, creatinine, and tumor markers carcinoembryonic antigen and CA19-9 are included in routine tests. Colonoscopy is performed once a year for two years. Computed tomography (CT) of chest and abdomen is performed at 6, 12, 18, and 24 months. Additional tests are scheduled at the discretion of the oncologist (e.g., a PET scan will be offered if CT gives a suspicious finding). Recurrences are diagnosed relying on clinical or radiological findings (most commonly CT) and will be proven pathologically whenever feasible. Withdrawal from the trial for any reason is permitted for all patients.

Outcome parameters

Primary endpoint

The primary end point is a composite of major complications during surgery or within 90 days after surgery. Major intraoperative and postoperative complications are defined as surgical or medical complications with a Common Terminology Criteria for Adverse Events (CTCAE) grade of III or higher. The primary end point is classified by the most severe complication in a patient.

2.7.2. Secondary endpoints

- Conversion to laparoscopic or open surgery: Conversion is defined as the use of laparoscopic port/ports for the anastomosis, or a laparotomy wound for any part of the mesocolon dissection or the anastomosis.
- Concentration of C-Reactive Protein (CRP): CRP values on postoperative day (POD) 1 and 3.
- Concentration of procalcitonine (PCT): PCT values on POD 1 and 3.
- Complete pathological assessment of complete mesocolic excision (CME) specimens: CME is defined as complete resection of the mesocolon with its anatomical envelope. Benchmarks of operative quality for CME comprise meticulous dissection in the embryological plane aiming to remove a complete mesocolic envelope containing the intact mesentery and all lymphatic, vascular, and neural tissue in tumor drainage area; central vascular ligation ensuring lymph nodes to be removed around the superior/inferior mesenteric vessels; and a sufficiently long portion of bowel (a minimum of 10 cm proximally and distally of the tumor) being resected to ensure the removal of any involved pericolic lymph nodes [24–28]. Rate of complete and near-CME achieved with hvNOTES is evaluated, based on standard pathologic assessment of CME specimens.
- Postoperative pain assessed by the numeric rating scale (NRS): The investigator's staff will provide a rating scale to the patients to self-rate and record their pain before surgery, at 24, 48, 72, 96, 120, 144, and 168 h after the procedure (or discharge if earlier) by using the NRS where 0 is for no pain and 10 is for the worst pain imaginable.

- Amount of narcotic pain medication administered: The amount of narcotic pain medication (total dose of morphine equivalent during hospitalization and average dose per day) administered through POD 7 (or discharge if earlier) will be recorded.
- Time to first flatus after surgery: Time to first flatus is defined as days from a colectomy procedure to first occurrence of flatus during recovery.
- Number of harvested lymph nodes: According to the pathological report, the number of harvested lymph nodes will be recorded.
- R0 resection: Rate of resection with negative margins during the surgical procedure according to the pathological report.
- Length of hospital stay: Number of days in the hospital after surgery.
- Sexual function assessment: Patient self-reported sexual functions as assessed by the Female Sexual Function Index (FSFI), before surgery, at 6 and 12 months after surgery. The 19-item FSFI is a questionnaire to rate sexual function between 2.0 and 36.0, in which 2.0 indicates low sexual function and 36.0 indicates high sexual function.
- Quality of recovery: The Quality of Recovery 40 questionnaire (QoR-40, score range: 40–200) will be administered to assess patient's quality of recovery at 14 days after surgery. Higher values show better outcomes. QoR is measured with the validate questionnaire by evaluating patients' comfort, emotions, physical independence, and support.
- Satisfaction with surgical scars: The patient's perception of scarring will be assessed using a validated questionnaire Patient Scar Assessment Questionnaire (PSAQ, score range: 28–102) at 3, 6, and 12 months after surgery. The PSAQ consists of 5 subscales: Appearance, symptoms, consciousness, satisfaction with appearance, and satisfaction with symptoms, in which lower values represent better outcomes.
- Quality of life: The Quality of Life Questionnaire (QLQ) of the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 Score will be administered to assess patient's quality of life at 3 months and 1 year after the procedure. The questionnaire has functional, global health, and symptoms subscales/items all scored from 0 to 100, in which higher scores represent high level of functioning, high quality of life, and high level of symptomatology, respectively.
- Postoperative recurrence patterns: Patterns of recurrence are determined according to the primary involved site and organ diagnosed with radiological tests (CT, US, MRI, or PET-CT), or with histologic proof (ascitic cytology, colonoscopic biopsy, or surgery).
- Relapse-free survival (RFS): RFS is defined as the time interval between surgery and the first recurrence (local, regional, distant), second cancer or death.
- Overall survival (OS): OS is defined as the time between surgery and death from any cause.

2.8. Data collection and data management

Outcomes will be collected in all patients who undergo hvNOTES. All baseline clinicopathological characteristics and clinical outcomes are prospectively collected and captured using an electronic case report form (eCRF) by local investigators. Appropriate data integrity including coding, security, and storage is ensured by the tracking system for eCRF. The coordinating investigator (JR) will collect questionnaires, laboratory tests, and radiological examinations throughout the study and all data will be centrally analyzed after study completion. Plans of promoting data quality, participant retention and complete follow-up are not specified a priori. An independent trained monitor will monitor on correctness of data management. The best way to handle missing data will be discussed with a statistician.

2.9. Data monitoring

Interim analysis will be performed after 28 procedures. The study will be terminated or temporarily halted for evaluation and potential adaption of the protocol after the interim analysis if CTCAE grade $\geq$ III, directly related to hvNOTES, is observed more than 4 patients. Furthermore, if more than one CTCAE grade V directly related to hvNOTES occurs during the study, the study will be directly terminated. These interim results are only accessible for the coordinating investigators and the principal investigator (TF). The final decision to terminate or continue the study is made by the principal investigator (TF). No data monitoring committee is needed given the clear stopping rules and the low expected complication rates of hvNOTES.

2.10. Harms

All serious adverse events (SAEs) and suspected unexpected serious adverse reactions (SUSARs) will be reported to the coordinating investigator within 24 h by the local investigators, and to the ethics committee within 7 days of first knowledge for lethal or life-threatening SAEs/SUSARs, and within 15 days for other SAEs/SUSARs by the coordinating investigator. From enrolment up to 4 weeks after the surgery is the time window for reporting SAEs/SUSARs.

2.11. Auditing

The study will be audited by an independent qualified monitor according to the local guidelines of the study centers. This means that participating centers are audited at least twice a year, depending on enrolment, with 100% auditing of the study master file, investigator site files, informed consent forms, eligibility criteria, source data verification and SAEs/SUSARs.

2.12. Statistical methods

2.12.1. Sample size

The hypothesis for the primary endpoint is that the total major perioperative complication rate from hvNOTES will not significantly exceed the standard laparoscopic surgery. The background total major postoperative complication rate from standard laparoscopic surgery was estimated to be 3% [29]. The margin of noninferiority was 10%, which was based on clinically and statistically meaningful differences as well as ethical criteria, cost, and feasibility. The sample size of 49 women was calculated to be sufficient (with a one-sided α risk of 0.05 and 80% power) to establish noninferiority. Allowing for 10% dropout, we aim to recruit 55 patients for this study.

2.12.2. Statistical analysis

Descriptive statistics using frequencies and percentages for qualitative variables, means and standard deviations or medians and interquartile ranges for quantitative variables depending on distributions are used to present patients' characteristics and outcomes. To compare repetitive quantitative data, the Mann-Whitney *U* test, Wilcoxon signed-rank test, the paired samples *t*-test, the Friedman test or repeated measures analysis of variance are used where appropriate. To compare repetitive categorical data, the McNemar test, the Wilcoxon signed-rank test, the Cochran's Q test or generalized estimating equations are used where appropriate. Time-to-event variables (i.e., RFS and OS) are estimated and displayed by using the Kaplan-Meier analysis. Descriptive statistics are used for other outcomes' analyses. All statistical tests are two-sided and $P < 0.05$ is considered statistically significant.

12.13. Patient and public involvement

Neither patients nor the public will be involved in construction of this study.

2.14. Study status and timeline

The study was open for enrollment in October 2019 with the first patient enrolled in December 2019 at Renmin Hospital of Wuhan University. At the time of this publication, 20 patients have participated in this trial and undergone hvNOTES. Because of the influence caused by pandemic of COVID-19, the enrollment is affected at the other 5 sites. It is estimated that enrollment will be completed by the end of 2024 pending the situation of COVID-19.

2.15. Ethics and dissemination

This study was approved by the local ethics committees (i.e., the Research Ethics Committee, Renmin Hospital of Wuhan University on Oct 12, 2019 [No. 2019-X2-11]; the Research Ethics Committee, Daping Hospital of Army Medical University on September 14, 2021 [No. 2021-130]; the Research Ethics Committee, The Second Affiliated Hospital of Zhejiang on October 20, 2021 [No. 2021-022]; the Research Ethics Committee, Qingdao Municipal Hospital on September 1, 2022 [No. 2022-NT007]; the Research Ethics Committee, Beijing Friendship Hospital of Capital Medical University on September 21, 2022 [No. 2022-P2-264-02]), and will be approved by the local ethics committee of the last one site before starting patient accrual at each hospital. Current protocol version (V2.1) approval was received on Jun 16, 2022 (No. WDRY2022-K053) at Renmin Hospital of Wuhan University. It will be conducted according to the declaration of Helsinki and in compliance with the Good Clinical Practice. Written informed consent will be obtained from all patients participating in this study (see online supplemental file). Important protocol modifications are communicated to all investigators, the Ethics Committees, and trial registries. The new protocol has to be approved by the Ethics Committees before it is implemented. The investigator has a liability insurance that provides cover for manage to participants through health injury caused by the study. Adequate medical treatment will be given to participants who suffer harms.

The authorship guidelines of International Committee of Medical Journal Editors will be followed for authorship eligibility. The results of this trial will be disseminated in academic conferences and peer-reviewed medical journals. The manuscript will be reviewed and approved by all authors before publication.

3. Discussion

In 2000, Kalloo et al. gave a presentation on the feasibility of a transgastric approach to the peritoneal cavity for liver biopsy in a porcine model at Digestive Disease Week, which was published 4 years later [30]. Rao and Reddy produced a video footage in 2004, demonstrating the transgastric approach to appendectomy and fallopian tubal ligation is feasible in a human patient [31]. Since then, many centers have reproduced these results and shown the validity of NOTES technique.

The most major concerns associated with NOTES are violating an innocent second organ and secure closure of the breached wall of the organs in order to gain access to the peritoneum or other body spaces [32,33]. A leakage from stomach, colon, rectum, or bladder could lead to severe complications [34]. However, there is no proven reliable technique for secure closure of these organ walls at present [32]. The transvaginal access has been used for diagnostic or therapeutic purposes by gynaecologists for more than 100 years, thus being well established and accepted [35]. The vaginal route virtually eliminates the concern for leakage [36]. Likewise, colpotomy-related complication rate is low, and closure of vaginal stump is easy to perform, safe, and secure. Currently, transvaginal access has actually been used by most NOTES procedures [37].

To date, due to technical limitations of pure NOTES or for safety reasons also, most clinical case reports have used a hybrid approach that accesses the abdominal cavity through vagina [10,16,18,38,39]. Technical limitations of pure NOTES include difficult to execute a safe full-thickness closure of viscerotomy, absence of triangulation of instruments, and lack of adequate tissue retraction, etc., which can be overcome with the laparoscopic assistance [40]. In colorectal surgery, hybrid procedure with abdominal laparoscopic assistance is still a useful if not essential appendage, at least to assist with visualization and retraction. This is particularly important in colon cancer cases that require mobilization of splenic or hepatic flexure, and wide tissue retraction to access the mesenteric base of major calibre vessels for high ligation.

To the best of our knowledge, four randomized controlled trials (RCTs) have compared hvNOTES to laparoscopic surgery for cholecystectomy [41–44]. Through the vagina, one study used a flexible endoscope [41] and one study used either a flexible or a rigid endoscope [43], while other two RCTs used a rigid one [42,44]. Rigid endoscopes and instruments seem to be favorable for surgeons, as both are common in surgical practice. These elegant studies showed that hvNOTES is not inferior in safety and effectiveness, but with a superior aesthetic result as compared to traditional laparoscopic surgery.

A study compared vNOTES (hybrid and pure) with laparoscopic surgery by means of meta-analysis of major clinical outcomes [45]. In this study, two RCTs and 11 non-randomized trials with an overall number of 1340 patients were included. Surgical procedures were cholecystectomy in 10 studies, adnexectomy in 2 studies, and appendectomy in one study. Risk of intraoperative and postoperative complications was comparable between vNOTES and traditional laparoscopy groups (1.2% vs. 2.3% and 4.1% vs. 6.2%, respectively). Other than this, the vNOTES group showed a significant lower postoperative pain score and shorter time of recovery. Despite early vehement resistant it was rapidly demonstrated that results of the hvNOTES were at least as good as those of laparoscopic approach, but suggesting superior clinical outcomes in terms of better cosmetic results, decreased rates of incisional complications, shorter hospital stay, less postoperative pain, and reduced amount of narcotic pain medication administered [9,10,45,46].

With regards to colon cancer surgery, clinical evidence for hvNOTES procedure is limited to case reports and case series. The radical resection of sigmoid colon cancer using the hvNOTES technique was described for the first time in 2008 [17]. By combining transvaginal with minilaparoscopic approaches synergistically, they removed a T3N1 sigmoid adenocarcinoma from a 78-year-old female. No complications were observed. This technique was also preferred by Moloney and Gan [21]. Colectomy by hvNOTES were performed in three patients with colon cancer and one patient with colon adenoma. All patients showed an early return of gastrointestinal function, low consumption of analgesics, and no morbidity related to transvaginal access. The short-term oncological outcomes were comparable to the published literature. Alba Mesa et al. reported a case series of 21 patients with sigmoid colon cancer in 2014 [38]. All patients underwent hvNOTES successfully and there was no need of conversion. All ambulated and 18 of them tolerated a liquid diet within 24 h after surgery. The patient self-rate NRS score was quite low with 1.8 at 24 h and 1.1 at 48 h after surgery. The median length of stay after surgery was 6 days, longer than the reported results of laparoscopic colectomy, which could be explained by the experimental nature of hvNOTES and the reluctance of the surgeons for early discharge. No intraoperative complications were observed. Only 6 patients experienced grade I or II Dindo-Clavien postoperative complications (including 1 case with ileus, 2 cases with vaginal discharge, and 3 cases with urinary tract infection), and only one patient presented grade III complication (trocar site hernia). At the 6 months after surgery follow-up, all 7 sexually active patients reported no change in sexual activity as compared with preoperative state. The pTNM staging was stage I in 13 patients and stage IIA in 8 patients. None of them had recurrent disease after a median follow-up of 25 months.

Bulian et al. analyzed the first 139 colonic procedures of the German 、 NOTES Registry, in which most procedures were conducted in hvNOTES (87.8%, 122/139) and with a rigid endoscope (98.6%, 137/139) [18]. In the hvNOTES group, there were 11 colon cancer cases and 111 benign lesion cases. Conversions to laparoscopic approach were necessary in 5 patients (4.1%). Intraoperative complications were recorded in 3.3% and postoperative complications in 12.3%. Conversion and complication rates were comparable to or even lower than those of laparoscopic colon surgery. They concluded that hvNOTES was feasible in colon operations, and most frequently used for sigmoid resection.

Because all high-level evidence of hvNOTES was from benign diseases, it's still controversial for the treatment of malignant tumors. Transcoelomic dissemination of tumor cells to peritoneal cavity or incision of natural orifice organ by insufflation or manipulation is one of the major concerns and matters for discussion. Considering frequency of peritoneal dissemination after surgery was less than one percent for patients with pT3 tumor, and pT4 was an independent risk factor for local recurrence and peritoneal carcinomatosis of patients with colon cancer who underwent curative surgery, [47,48] we set cT1-3 as one of the inclusion criteria to minimize potential tumor seeding during surgery. Postoperative recurrence patterns and RFS will be observed as secondary endpoints to evaluate the real rates of dissemination after hvNOTES.

Limitations of this study include the small sample size with absence of a control group and the broad eligibility criteria for the study population, which allows the enrolment of patients with both left and right colon cancers, as well as including distinct pathological features. Furthermore, varying postoperative systemic regimens are allowed, which might result in heterogeneity of clinical outcomes. These clinical and pathological heterogeneity could impede the interpretation of preliminary efficacy results.

Apparently, NOTES did not result in a vivid upheaval of MIS. Prior high prospects regarding its application declined for the difficulties stumbled at present time, which results in an expiring interest for this topic – also apparent in decreasing numbers of publications on this procedure [49]. With NOTES being a novel approach, success on it relies on the surgeon's comfort level as well as evolving technology to make this approach easier [50]. Further development of new platforms and instruments (e.g., the single-port robot [51], and the flexible endoscopic robot [52]) adaptive to NOTES would boost efforts toward clinical applications for this technique. While these are becoming accomplished, equal endeavor and effort should be applied in determining appropriate indications for this novel intervention.

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Patient consent for publication

Not required.

Provenance and peer review

Not commissioned; externally peer reviewed.

Author contribution statement

Conceived and designed the experiments: Tao Fu.
Performed the experiments: Tao Fu; Hongwei Yao; Lifeng Sun; Xiaorong Li and Weidong Tong.
Analyzed and interpreted the data: Tao Fu; Jun Ren; Bin Huang; Hongwei Yao; Lifeng Sun; Xiaorong Li and Weidong Tong.
Contributed reagents, materials, analysis tools or data: Tao Fu; Jun Ren and Bin Huang.
Wrote the paper: Tao Fu; Jun Ren; Bin Huang; Hongwei Yao; Lifeng Sun; Xiaorong Li and Weidong Tong.

Data availability statement

No data was used for the research described in the article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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None.

Appendix ASupplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e20187.

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