LAPAROSCOPIC SURGERY IN COLORECTAL CANCER

EDITED BY: Xi Cheng and Ren Zhao

PUBLISHED IN: Frontiers in Oncology and Frontiers in Surgery

frontiers Research Topics

ISSN 1664-8714
ISBN 978-2-83250-220-4
DOI 10.3389/978-2-83250-220-4

About Frontiers

Frontiers is more than just an open-access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers Journal Series

The Frontiers Journal Series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the Frontiers Journal Series operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to Quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews.
Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the Frontiers Journals Series: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area! Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers Editorial Office: frontiersin.org/about/contact

LAPAROSCOPIC SURGERY IN COLORECTAL CANCER

Topic Editors:
Xi Cheng, Shanghai Jiao Tong University, China
Ren Zhao, Shanghai Jiao Tong University, China

Citation: Cheng, X., Zhao, R., eds. (2022). Laparoscopic Surgery in Colorectal Cancer. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-83250-220-4

Table of Contents

frontiers | Frontiers in Oncology

TYPE Editorial
PUBLISHED 01 September 2022
DOI 10.3389/fonc.2022.960730

Check for updates

OPEN ACCESS

EDITED AND REVIEWED BY
Giovanni Battista Levi Sandri, Ospedale di Cassino, Italy

*CORRESPONDENCE
Xi Cheng
drchengxi@126.com
Ren Zhao
rjzhaoren@139.com

SPECIALTY SECTION
This article was submitted to Surgical Oncology, a section of the journal Frontiers in Oncology

RECEIVED 03 June 2022
ACCEPTED 01 August 2022
PUBLISHED 01 September 2022

CITATION
Jia W, Cheng X and Zhao R (2022) Editorial: Laparoscopic surgery in colorectal cancer. *Front. Oncol.* 12:960730. doi: 10.3389/fonc.2022.960730

Editorial: Laparoscopic surgery in colorectal cancer

Wenqing Jia[1,2], Xi Cheng[1,2]* and Ren Zhao[1,2]*

[1]Department of General Surgery, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China, [2]Shanghai Institute of Digestive surgery, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

KEYWORDS

single incision laparoscopic surgery, robot-assisted surgery, colorectal cancer, laparoscopic surgery, editorial

Editorial on the Research Topic
Laparoscopic surgery in colorectal cancer

Laparoscopic surgery for colorectal cancer has evolved quickly and enthusiastically applied in clinical works for almost two decades (1). Regular laparoscopic colorectal surgery usually need four or five incisions, in recent years, efforts have been spent to further minimize the trauma, reduce postoperative pain, and improve cosmetic effect (2). Innovations like natural orifice transluminal endoscopic surgery (NOTES), transanal total mesorectal excision (taTME), robotic surgery, and single incision laparoscopic surgery (SILS) has been developed to reach the goal of "scarless" surgery, which represents the state-of-the-art phenomenon in the field (3, 4). Additionally, burgeoning instruments, single-incision port devices, and robot platforms open up a new scenario of CRC surgery (5, 6).

Under this circumstance, this Research Topic collected 9 scientific studies focused on surgical methods and experience of minimally invasive surgery, especially single incision laparoscopic surgery (SILS) and robotic surgery.

A growing knowledge has revealed that port subtraction benefits CRC patients in multiple aspects without a sacrifice of operative and oncology safety. Zhang et al. proved that laparoscopic right hemicolectomy (LRC) conducted through three ports harvested more lymph nodes and caused less blood loss compared with LRC performed with five ports in a retrospective clinical trial. Port-reduced surgery demonstrated a latent advantage in long-term outcomes such as overall survival (OS), which required more convincing evidence. According to a well-designed randomized controlled trial conducted by Song et al. in 193 CRC patients, SILS performed by experienced surgeons reduced postoperative pain and depicted good short-term outcomes as well as cosmetic effects compared with conventional laparoscopic surgery. The long-term outcomes and complications of SILS such as incisional hernia are expected to be revealed in sequential research with a low loss of follow-up rate and high quality of evaluation.

The transanal approach has also been developed with the aim of minimizing vulnus. Despite mini-residual risks, transanal endoscopic microsurgery (TEM) is a choice for early-stage rectal cancer. Tang et al. have launched the first prospective multicenter randomized trial to compare the risk of local recurrence and total survival of TEM followed by radiotherapy and TME in T2N0M0 distal rectal cancer patients. Guo et al. summarized the evolution and narrated the latest research status of taTME, a surgery that provided an accurate exposure of the mesorectal plane and direct vision of the distal resection margin. They also analyzed the disputations about taTME and provided a dialectical view on its future.

Regardless of multiple approaches to CRC surgery, dissection of No.253 lymph nodes to a certain extent and preservation of autonomic nerve is a shared issue, with all schools of thought contending for attention. Zheng et al. proposed a novel technique for nerve-sparing high ligation of the inferior mesenteric artery (IMA) called intrasheath separation of the IMA and partial preservation of the left IMA sheath along with the left trunk of the inferior mesenteric plexus (IMP), based on anatomical evidence of the spatial relationship between IMA and IMP. While Li et al. believe that the IMP nerve plane can be separated from IMA by enforcing traction and anti-traction, also it is identified as the dorsal border of station 253 nodes, thus creating a "nerve plane orientation" technique. Both of them have heuristic value in avoidance of postoperative urogenital dysfunction caused by latent autonomic nerve damage in surgery.

Wang et al. took an in-depth look at the quality of surgical resection in laparoscopic, robotic, and transanal total mesorectal excision for mid-/low rectal cancer, by means of a Bayesian network meta-analysis. This systemic review prompt researchers to deepen their insight into the pros and cons of various minimally invasive surgical approaches and facilitate clinical decision-making.

Postoperative medical care and timely intervention of other adjuvant therapies are also significant for patient recovery. Wang et al. disclosed the significant role of enhanced recovery after surgery (ERAS) as an "icing on the cake" combined with SILS, leading to earlier dietary resumption and shorter hospital stays of CRC patients after SILS. Kumara et al. discovered a phenomenon in which keratinocyte growth factor (KGF), an FGF family protein mainly produced by mesenchymal cells, is elevated significantly for a 5-week course after minimally invasive colorectal resection probably as a consequence of acute inflammatory response and wound-healing. However, its latent role in tumor recurrence and metastasis raises the question of whether perioperative anticancer treatments are essential and feasible, and this deserves further exploration.

In a nutshell, the papers included in this Research Topic describe the brand-new development of laparoscopic surgery in colorectal cancer. We'd like to express our sincere gratitude to all authors, editors, and reviewers of all these publications, as well as the editorial team at Frontiers for their devotion and assistance in the process of reviewing and publishing this Research Topic. The future trend points to a combination of SILS and robotic surgical platform, and the next decade promises to illuminate more in-depth aspects of "scarless" surgery in colorectal cancer treatment.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Jacob BP, Salky B. Laparoscopic colectomy for colon adenocarcinoma: An 11-year retrospective review with 5-year survival rates. *Surg Endosc* (2005) 19(5):643–49. doi: 10.1007/s00464-004-8921-y

2. Pelosi MA, Pelosi MA. Laparoscopic hysterectomy with bilateral salpingo-oophorectomy using a single umbilical puncture. *N J Med* (1991) 88(10):721–26.

3. Cianchi F, Staderini F, Badii B. Single-incision laparoscopic colorectal surgery for cancer: state of art. *World J Gastroenterol* (2014) 20(20):6073–80. doi: 10.3748/wjg.v20.i20.6073

4. Diana M, Dhumane P, Cahill RA, Mortensen N, Leroy J, Marescaux J. Minimal invasive single-site surgery in colorectal procedures: Current state of the art. *J Minim Access Surg* (2011) 7(1):52–60. doi: 10.4103/0972-9941.72382

5. Dhumane PW, Diana M, Leroy J, Marescaux J. Minimally invasive single-site surgery for the digestive system: A technological review. *J Minim Access Surg* (2011) 7(1):40–51. doi: 10.4103/0972-9941.72381

6. Rondelli F, Sanguinetti A, Polistena A, Avenia S, Marcacci C, Ceccarelli G, et al. Robotic transanal total mesorectal excision (RTaTME): State of the art. *J Pers Med* (2021) 11(6): 584. doi: 10.3390/jpm11060584

frontiers in Oncology

ORIGINAL RESEARCH
published: 24 June 2021
doi: 10.3389/fonc.2021.694059

Check for updates

An Intrasheath Separation Technique for Nerve-Sparing High Ligation of the Inferior Mesenteric Artery in Colorectal Cancer Surgery

Zhifang Zheng[1,2†], Xiaojie Wang[1,2†], Ying Huang[1,2], Xingrong Lu[1,2], Xiaozhen Zhao[3] and Pan Chi[1,2*]*

[1] Department of Colorectal Surgery, Fujian Medical University Union Hospital, Fuzhou, China, [2] Department of General Surgery, Fujian Medical University Union Hospital, Fuzhou, China, [3] Laboratory of Clinical Applied Anatomy, Fujian Medical University, Fuzhou, China

OPEN ACCESS

Edited by:
Xi Cheng,
Shanghai Jiao Tong University, China

Reviewed by:
Baochi Ou,
First Affiliated Hospital of Anhui Medical University, China
Xiaonan Shen,
Shanghai JiaoTong University, China

****Correspondence:***
Pan Chi
chipan363@163.com
Xiaozhen Zhao
zxz8338@163.com

†These authors have contributed equally to this work and share first authorship

Specialty section:
This article was submitted to Surgical Oncology, a section of the journal Frontiers in Oncology

Received: *12 April 2021*
Accepted: *08 June 2021*
Published: *24 June 2021*

Citation:
Zheng Z, Wang X, Huang Y, Lu X, Zhao X and Chi P (2021) An Intrasheath Separation Technique for Nerve-Sparing High Ligation of the Inferior Mesenteric Artery in Colorectal Cancer Surgery. Front. Oncol. 11:694059. doi: 10.3389/fonc.2021.694059

Purpose: To investigate the relationship between the left trunk of the inferior mesenteric plexus (IMP) and the vascular sheath of the inferior mesenteric artery (IMA) and to explore anatomical evidence for autonomic nerve preservation during high ligation of the IMA in colorectal cancer surgery.

Methods: We evaluated the relationship in 23 consecutive cases of laparoscopic or robotic colorectal surgery with high ligation of the IMA at our institute. Anatomical dissection was performed on 5 formalin-fixed abdominal specimens. A novel anatomical evidence-based operative technique was proposed.

Results: Anatomical observation showed that the left trunk of the IMP was closely connected with the IMA and was involved in the composition of the vascular sheath. Based on anatomical evidence, we present a novel operative technique for nerve-sparing high ligation of the IMA that was successfully performed in 45 colorectal cancer surgeries with no intraoperative complications and satisfactory postoperative urogenital functional outcomes.

Conclusion: The left trunk of the IMP is involved in the composition of the IMA vascular sheath. This novel anatomical evidence-based operative technique for nerve-sparing high ligation of the IMA is technically safe and feasible.

Keywords: colorectal cancer, high ligation, inferior mesenteric artery (IMA), inferior mesenteric plexus, vascular sheath

INTRODUCTION

Ligation of the inferior mesenteric artery (IMA) is a key procedure during surgery for left colon and rectal cancer. Ligation of the IMA from the origin of the aorta is defined as high ligation, and ligation below the origin of the left colic artery is defined as low ligation (1). Based on oncological, technical, and anatomical considerations, the location of IMA ligation is still controversial. Although there is no consistent evidence that high ligation of the IMA has a survival benefit

(2–4), it may improve the lymph node dissection rate (5) and tumor staging accuracy (3). Although high ligation of the IMA results in a decreased blood supply to the distal colon (6, 7), it simultaneously contributes to low anastomosis with no tension during low anterior resection for rectal cancer (2, 8). In fact, there is no significant difference in the incidence of anastomotic leakage between high and low ligation of the IMA (9, 10). With the popularity of laparoscopic surgery, laparoscopic high ligation of the IMA is much easier than low ligation and is not associated with a prolonged operation or an increase in blood loss (11). Therefore, high ligation of the IMA is still preferred by most surgeons in colorectal cancer surgery.

However, it is widely accepted that high ligation of the IMA carries a risk of damage to the surrounding autonomic nerve plexuses (12, 13), which may lead to postoperative urogenital dysfunction (14). The reason is that the bilateral trunks of the inferior mesenteric plexus (IMP) pass through the root of the IMA. At present, anatomical studies of the relationship between the root of the IMA and the autonomic nerve plexus are very limited. Previous studies (15–17) have shown that the right trunk of the IMP is located relatively far from the root of the IMA and does not cross the root of the IMA, while the left trunk of the IMP crosses over the IMA (**Figure 1**). Therefore, high ligation of the IMA may be more likely to cause damage to the left trunk of the IMP. It is well known that the IMA is wrapped in a vascular sheath. Unfortunately, the anatomical relationship between the left trunk of the IMP and the IMA vascular sheath has not been reported.

Therefore, the present study aimed to investigate the anatomical relationship between the left trunk of the IMP and the IMA vascular sheath, providing anatomical evidence for autonomic nerve preservation in high ligation of the IMA in colorectal cancer surgery.

MATERIALS AND METHODS

Samples

To investigate the relationship between the IMP and the IMA vascular sheath, we prospectively collected clinicopathological data and surgical videos of 23 consecutive cases of laparoscopic or robotic colorectal surgery with high ligation of the IMA at our

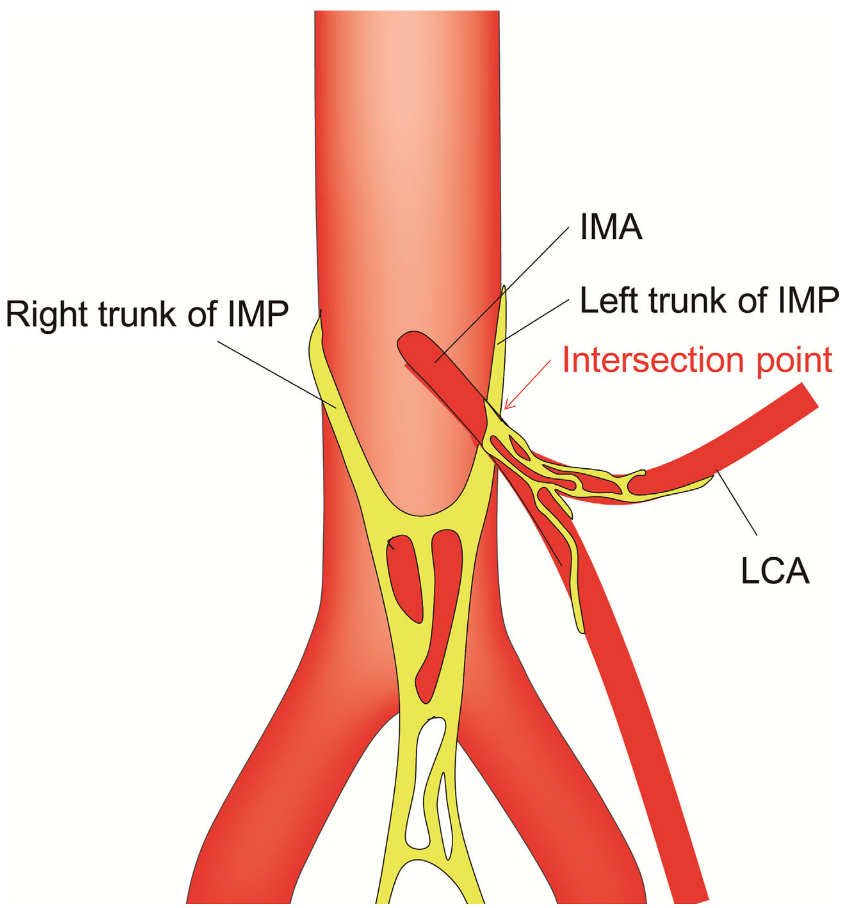


FIGURE 1 | Schematic representation of the relationship between the IMA and the surrounding autonomic nerve plexuses. IMP, inferior mesenteric plexus; IMA, inferior mesenteric artery; LCA, left colic artery.

institution in October 2019. Five formalin-fixed cadavers (3 males and 2 females; mean age, 72.3 years) donated to Fujian Medical University were dissected with the assistance of binocular loupes. Cadavers with a deformed anatomy in the region of the IMA resulting from a previous abdominal surgery were excluded.

From January 2020 to February 2020, based on the anatomical results, a novel operative technique for nerve-sparing high ligation of the IMA was performed in laparoscopic or robotic surgery for 45 patients with advanced colorectal cancer by an experienced colorectal surgeon (Prof. Pan Chi) at the Fujian Medical University Union Hospital. The reliability of the anatomical evidence and the key points of the surgical techniques were evaluated. The operative procedures were recorded on video. Informed consent was obtained from all participating patients. This study was approved by the Institutional Review Board of the Fujian Medical University Union Hospital (no. 2020KY092).

Definition of the IMA Sheath

The IMA vascular sheath was defined as the tissue located between the surface of the IMA adventitia and the collagenous layers isolated from adipose tissue coupled with the surrounding connective tissue, including layers of the autonomic nerve plexus, adipose tissue, collagenous fibers, and microvessels (18, 19).

Urogenital Function

The patients' urinary functional status was evaluated by the International Prostate Symptom Score (IPSS). Erectile function was evaluated by the 5-item version of the International Erectile Function Index Questionnaire (IIEF-5) (20). The total IIEF-5 score ranged from 1 to 25, with a lower score indicating more severe erectile dysfunction.

Statistical Analysis

No statistical analysis was necessary.

RESULTS

Anatomical Observations

We observed and evaluated the relationship between the IMP and the IMA vascular sheath in 23 patients who underwent laparoscopic or robotic colorectal surgery with high ligation of the IMA. The mean age of the enrolled patients was 58.2 ± 9.2 years old, with a male:female ratio of 1.5:1. The tumors were located in the left colon (n=3), sigmoid colon (n=5), and rectum (n=15). Regarding the stage classification, 5, 6, and 12 patients had stage I, II, and III disease, respectively. Among them, 8 patients received preoperative neoadjuvant therapy.

In all 23 patients, typical structural relationships were observed, as follows: the right trunk of the IMP was located relatively far from the root of the IMA and did not cross the root of the IMA, while the left trunk of the IMP was closely connected with the IMA and was involved in the formation of the IMA vascular sheath. The nerve fibers of the left trunk of the IMP could be raised with the IMA by pulling the IMA upward during the operation, similar to a "tent" (**Figure 2**). The anatomical relationships were further validated in formalin-fixed cadavers. The main right trunk of the IMP was located relatively far from the root of the IMA, while several tiny branches supplying the left colon along the IMA were observed (**Figure 3A**). The left

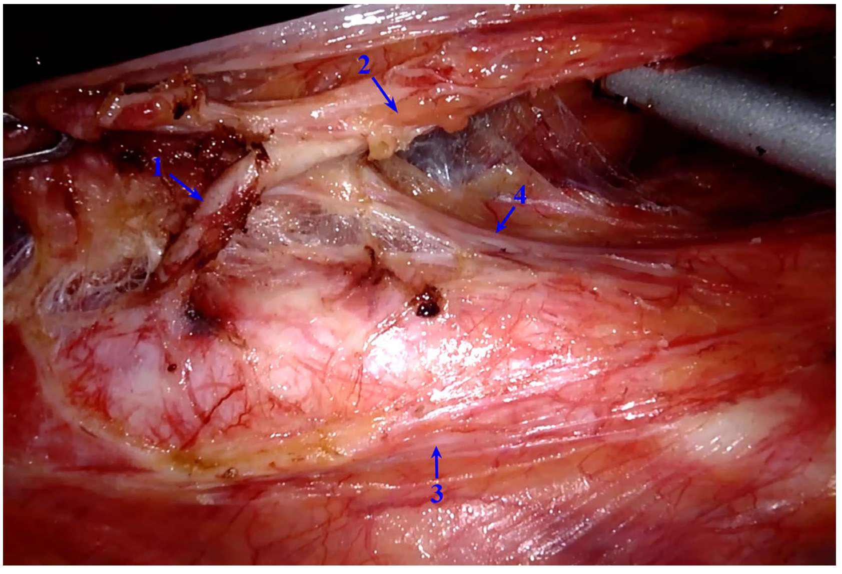


FIGURE 2 | Intraoperative image of the relationship between the IMA and IMP. The left trunk of the IMP is tightly connected to the IMA, forming part of the IMA vascular sheath. IMP, inferior mesenteric plexus; IMA, inferior mesenteric artery. 1, IMA without the vascular sheath; 2, IMA with the vascular sheath; 3, right trunk of the IMP; 4, left trunk of the IMP.

FIGURE 3 | Relationship between the IMA and IMP in formalin-fixed cadavers. **(A)** The left trunk of the IMP could not be removed from the IMA sheath in formalin-fixed cadavers. **(B)** The left trunk of the IMP could be separated from the IMA only when the IMA sheath was peeled off. IMP, inferior mesenteric plexus; IMA, inferior mesenteric artery. 1, IMA without the vascular sheath; 2, IMA with the vascular sheath; 3, right trunk of the IMP; 4, left trunk of the IMP; 5, branches from the main right trunk of the IMP to the left colon.

trunk of the IMP could not be removed from the IMA sheath in the formalin-fixed cadavers (**Figure 3A**). The left trunk of the IMP could be separated from the IMA only when the IMA sheath was peeled off (**Figure 3B**).

Anatomical Evidence-Based Surgical Technique

Based on the above anatomical evidence, we proposed a novel operative technique for nerve-sparing high ligation of the IMA called intrasheath separation of the IMA and partial preservation of the left IMA sheath along with the left trunk of the IMP (**Figures 4A–C**). The details of the surgical procedures are shown in the attached **video**. Briefly, the dissection commenced above the junction point of the bilateral trunks of the IMP with an incision in Gerota's fascia and exposure of the abdominal aorta. Along the surface of the abdominal aorta and the medial side of the right trunk of the IMP, the root of the IMA was exposed, and the no. 253 lymph nodes were dissected at the root of the IMA (**Figure 5A**). Subsequently, the right IMA vascular sheath was cut at the root of the IMA and peeled off slowly upward along the IMA (**Figure 5B**). Approximately 1.5 cm away from the root of the IMA, the left trunk of the IMP was cross-fused with the IMA vascular sheath. Starting from the root of the IMA, the left IMA vascular sheath was separated at the space between the left wall of the IMA and the left IMA vascular sheath until after the left trunk of the IMP had passed, and then the left IMA vascular sheath along with the left trunk of the IMP could be preserved (**Figure 5C**). Finally, the IMA was ligated and cut at its root (**Figure 5D**). **Figure 4D** shows representative postoperative specimens containing the right IMA vascular sheath, while the

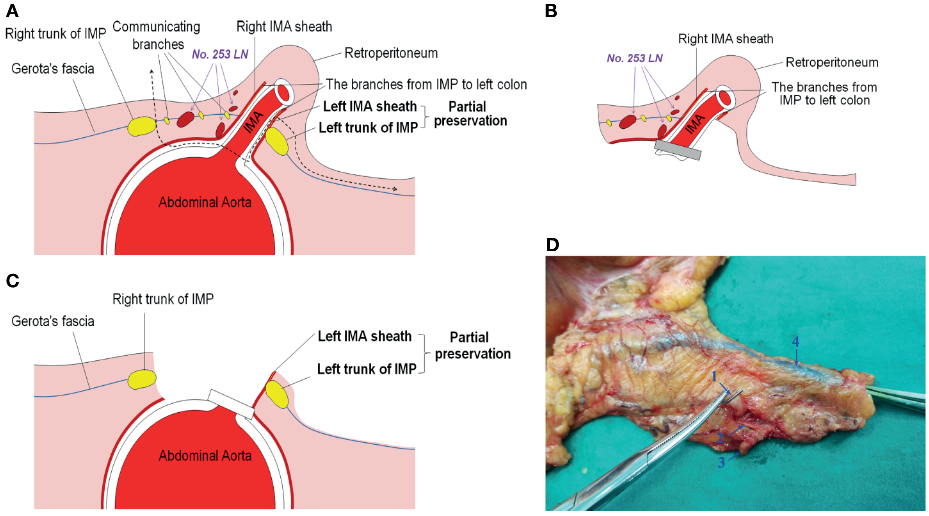


FIGURE 4 | Illustration of the novel operative technique for nerve-sparing high ligation of the IMA. **(A)** Schematic diagram of the novel operative technique: intrasheath separation of the IMA and partial preservation of the left IMA sheath along with the left trunk of the IMP. **(B)** Diagram of a portion that had been removed intraoperatively. **(C)** Diagram of a preserved part intraoperatively. **(D)** Representative specimen after application of the novel operative technique. IMA, inferior mesenteric artery; IMP, inferior mesenteric plexus. 1, IMA; 2, right IMA sheath; 3, enlarged lymph node; 4, inferior mesenteric vein.

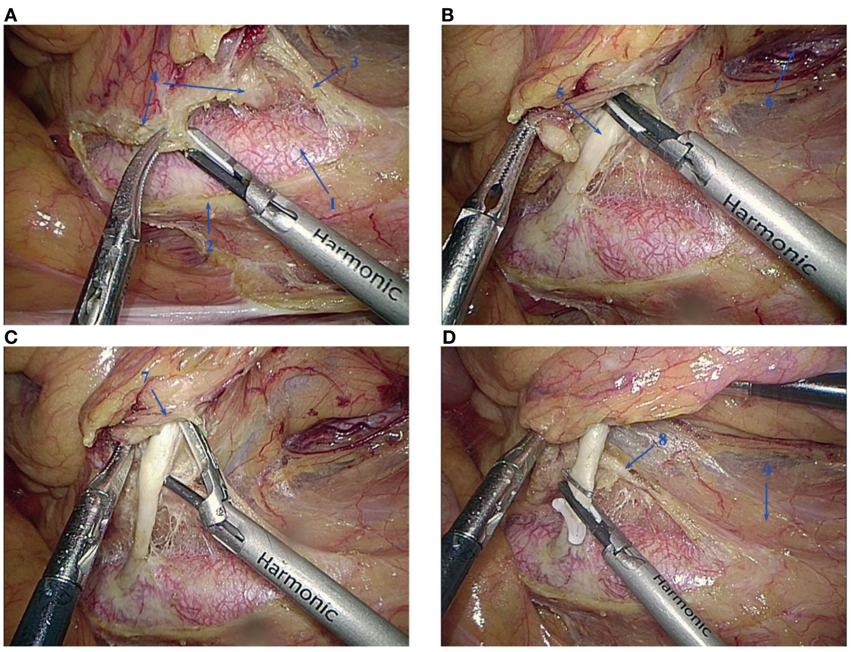


FIGURE 5 | Operative technique. **(A)** Lymph nodes around the root of the IMA are dissected in the nerve-free "window", and the root of the IMA is exposed. **(B)** From the right side of the root of the IMA, the vascular sheath is peeled off. **(C)** The left side of the IMA vascular sheath is preserved. **(D)** The IMA is ligated and cut at its root. IMA, inferior mesenteric artery; IMP, inferior mesenteric plexus. 1, Abdominal aorta; 2, right trunk of the IMP; 3, left trunk of the IMP; 4, lymph nodes; 5, IMA; 6, left ureter; 7, right vascular sheath of the IMA; 8, left vascular sheath of the IMA; 9, Gerota's fascia.

left IMA vascular sheath and the left trunk of the IMP were preserved. Several enlarged lymph nodes were visible in this specimen and were confirmed as metastatic lymph nodes by postoperative pathology.

Surgical Outcomes

The novel anatomical evidence-based operative technique for nerve-sparing high ligation of the IMA was successfully performed in 45 consecutive patients who underwent laparoscopic or robotic surgery for colorectal cancer. The clinicopathological data of the patients are presented in **Table 1**. The bilateral trunks of the IMP could be identified and well protected during the operation. The mean operative time from exposure of the abdominal aorta to high ligation of the IMA was 8.2 ± 2.1 min (range, 6-11 min). The mean blood loss during high ligation of the IMA was 5 ± 6.2 ml (range, 0-20 ml), without intraoperative complications. The preoperative IPSS and IIEF-5 score was 3.1 ± 2.1 and 18.7 ± 5.6, respectively, and the postoperative urogenital function was satisfactory (IPSS at 6 months postoperatively: 4.9 ± 3.6; IIEF-5 score at 12 months postoperatively: 17.1 ± 5.1).

DISCUSSION

With the improvement of oncological results (21), the quality of life of patients after colorectal cancer surgery has become increasingly important, and autonomic nerve preservation has gradually attracted the attention of surgeons and scholars (22). The root of the IMA is widely considered to be one of the critical areas for autonomic nerve damage during surgery (12, 13). However, anatomical studies on the relationship between the roots of the IMA and the surrounding autonomic nerves are limited, and there are still few reports on autonomic nerve-preserving surgical techniques for high ligation of the IMA based on reliable anatomical evidence. Therefore, the present study explored the relationship between the IMP (especially the left trunk of the IMP) and the IMA by anatomical observation. It was found that the left trunk of the IMP formed part of the IMA vascular sheath, and guided by anatomical evidence, a novel surgical technique for nerve-sparing high ligation of the IMA was proposed.

In this study, it was found that the main right trunk of the IMP did not cross the root of the IMA, and the left trunk of the IMP crossed over the IMA, which is consistent with previous studies (15–17). In contrast, previous anatomical studies of cadavers have neglected the existence of vascular sheaths. Intraoperatively, we found that the left trunk of the IMP formed part of the IMA vascular sheath, which was confirmed in formalin-fixed cadavers. This anatomical finding is important because it means that extrasheath separation of the IMA will inevitably cause damage to the left trunk of the IMP in the case of high ligation of the IMA, which may lead to postoperative urogenital dysfunction.

To protect autonomic nerves during surgery, several studies have presented different opinions. The results from a randomized controlled trial [HIGHLOW trial (23)] showed that low ligation of the IMA in laparoscopic anterior resection for rectal cancer reduced genitourinary dysfunction. Many studies have found that IMA lymph node metastasis is an important prognostic factor in patients with colorectal cancer (24–26). In the Japanese Society for Cancer of the Colon and

TABLE 1 | Clinical and pathological characteristics of participating patients.

Variable	Value
No. of cases	45
Age, mean (SD), years	62.0 ± 10.3
Sex (male/female)	30/15
Body mass index, mean (SD), kg/m^2	23.2 ± 2.6
Tumor site, n (%)	
Left colon	5 (11.1)
Sigmoid colon	9 (20.0)
Rectum	31 (68.9)
Differentiation, n (%)	
Well or moderate	39 (86.7)
Poor, mucinous or signet-ring cell	6 (13.3)
Neoadjuvant chemoradiotherapy, n (%)	
Yes	15 (33.3)
No	30 (66.7)
pTNM stage, n (%)	
I	11 (24.4)
II	14 (31.2)
III	20 (44.4)
Lymph nodes retrieved, mean (SD)	16.1 ± 8.9
Positive lymph nodes, mean (SD)	0.9 ± 1.3
Positive no. 253 lymph nodes, n (%)	3 (6.7)
Total operative time, mean (SD), min	185 ± 35.7
Operative time from exposure of the abdominal aorta to high ligation of the IMA, mean (SD), min	8.2 ± 2.1
Estimated blood loss, mean (SD), ml	78.9 ± 31.4
Estimated blood loss during high ligation of the IMA, mean (SD), ml	5 ± 6.2
IPSS	
Preoperatively	3.1 ± 2.1
Six months postoperatively	4.9 ± 3.6
IIEF-5 score	
Preoperatively	18.7 ± 5.6
Twelve months postoperatively	17.1 ± 5.1

SD, standard deviation; IMA, inferior mesenteric artery; IPSS, International Prostate Symptom Score; IIEF-5, International Index of Erectile Function 5.

Rectum (JSCCR) guidelines (27), lymph node dissection of the root of the IMA, namely, D3 lymph node dissection, is recommended for patients with preoperative clinical stage T2 disease or higher and rectal cancer with lymph node metastasis. The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines (28) recommend that patients suspected of having IMA lymph node metastasis should undergo high ligation and lymph node dissection of the root of the IMA. Therefore, low ligation of the IMA may not be appropriate in this subset of patients. Yang et al. (17) suggested that high ligation of the IMA should be performed at a distance distal to the intersection of the left trunk of the IMP and the IMA to protect the left trunk of the IMP. However, whether the no. 253 lymph nodes can be dissected completely by the above method and the subsequent oncological results still need further verification. Liang et al. (14) believed that the left trunk of the IMP should be adequately cleared from "behind" the IMA during surgery, but it was not separated *via* the intrasheath method, which would inevitably cause damage to the left trunk of the IMP to some extent. To maintain a balance between oncology and function, based on the anatomical findings of the present study, we proposed a novel surgical technique for nerve-sparing high ligation of the IMA called intrasheath separation of the IMA and partial preservation of the left IMA sheath along with the left trunk of the IMP. This method not only allows adequate dissection of the lymph nodes at the root of the IMA but also protects the left trunk of the IMP. This surgical technique was successfully performed in 45 patients undergoing surgery for colorectal cancer. The bilateral trunks of the IMP were well identified and protected intraoperatively, with no intraoperative complications and satisfactory postoperative urogenital functional outcomes. Therefore, this surgical technique is technically safe and feasible.

In addition, some scholars (16, 17) believe that the integrity of Gerota's fascia should be maintained to better protect the autonomic nerves below Gerota's fascia during lymph node dissection. However, we believe that creating an incision in Gerota's fascia above the junction point of the bilateral trunks of the IMP will facilitate lymph node dissection at the root of the IMA and thus yield better oncological results. Our previous study (24) showed that the rate of no. 253 lymph node metastasis in stage III rectal cancer was 11.0% (29/264). As the **Video** shows, if the integrity of Gerota's fascia is maintained, it is likely that the dissection of enlarged lymph nodes is not feasible or even omitted. In contrast, incising Gerota's fascia at a suitable position can better expose the IMP, which may, to some extent, help to achieve better nerve protection.

To the best of our knowledge, this study is the first to report the anatomical relationship between the left trunk of the IMP and the IMA vascular sheath and to propose a novel and reliable nerve-sparing surgical technique for high ligation of the IMA based on anatomical evidence. Due to the limitation of the relatively small sample size, the results need to be validated by further studies with large samples in the near future. Moreover, the oncological outcomes still need to be assessed with long-term follow-up.

CONCLUSION

The left trunk of the IMP forms part of the IMA vascular sheath. This novel anatomical evidence-based operative technique for nerve-sparing high ligation of the IMA is technically safe and feasible. However, further validation in larger studies is warranted.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Institutional Review Board of the Fujian Medical University Union Hospital (NO.2020KY092). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ZZ and XW conceived of the study, performed the anatomical studies, and prepared the manuscript draft. YH, XL, XZ, and PC critically revised the manuscript for important intellectual content. ZZ and XW performed the data collection and designed the study. All authors contributed to the article and approved the submitted version.

FUNDING

This study was supported by the Joint Funds for the Innovation of Science and Technology, Fujian Province (No. 2019Y9101), the Natural Science Foundation of Fujian Province (2020J011030), the Medical Science Research Foundation of Beijing Medical and Health Foundation (B20062DS), and the Medical Innovation Project of Fujian Province (2020CXA025).

ACKNOWLEDGMENTS

The authors are grateful to Prof. Chunpeng Chen and Geng Zhang for their assistance with the anatomical cadaver study.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2021.694059/full#supplementary-material

REFERENCES

1. Lowry AC, Simmang CL, Boulos P, Farmer KC, Finan PJ, Hyman N, et al. Consensus Statement of Definitions for Anorectal Physiology and Rectal Cancer: Report of the Tripartite Consensus Conference on Definitions for Anorectal Physiology and Rectal Cancer, Washington, D.C., May 1, 1999. *Dis Colon Rectum* (2001) 44:915–9. doi: 10.1007/BF02235475
2. Hida J, Okuno K. High Ligation of the Inferior Mesenteric Artery in Rectal Cancer Surgery. *Surg Today* (2013) 43:8–19. doi: 10.1007/s00595-012-0359-6
3. Titu LV, Tweedle E, Rooney PS. High Tie of the Inferior Mesenteric Artery in Curative Surgery for Left Colonic and Rectal Cancers: A Systematic Review. *Dig Surg* (2008) 25:148–57. doi: 10.1159/000128172
4. Singh D, Luo J, Liu X, Ma Z, Cheng H, Yu Y, et al. The Long-Term Survival Benefits of High and Low Ligation of Inferior Mesenteric Artery in Colorectal Cancer Surgery. *Medicine* (2017) 96:e8520. doi: 10.1097/MD.0000000000008520
5. Adachi Y, Inomata M, Miyazaki N, Sato K, Shiraishi N, Kitano S. Distribution of Lymph Node Metastasis and Level of Inferior Mesenteric Artery Ligation in Colorectal Cancer. *J Clin Gastroenterol* (1998) 26:179–82. doi: 10.1097/00004836-199804000-00006
6. Seike K, Koda K, Saito N, Oda K, Kosugi C, Shimizu K, et al. Laser Doppler Assessment of the Influence of Division at the Root of the Inferior Mesenteric Artery on Anastomotic Blood Flow in Rectosigmoid Cancer Surgery. *Int J Colorectal Dis* (2007) 22:689–97. doi: 10.1007/s00384-006-0221-7
7. Tsujinaka S, Kawamura YJ, Tan KY, Mizokami K, Sasaki J, Maeda T, et al. Proximal Bowel Necrosis After High Ligation of the Inferior Mesenteric Artery in Colorectal Surgery. *Scand J Surg* (2012) 101:21–5. doi: 10.1177/145749691210100105
8. Buunen M, Lange MM, Ditzel M, Kleinrensink GJ, van de Velde CJ, Lange JF. Level of Arterial Ligation in Total Mesorectal Excision (TME): An Anatomical Study. *Int J Colorectal Dis* (2009) 24:1317–20. doi: 10.1007/s00384-009-0761-8
9. Rutegård M, Hemmingsson O, Matthiessen P, Rutegård J. High Tie in Anterior Resection for Rectal Cancer Confers No Increased Risk of Anastomotic Leakage. *Br J Surg* (2012) 99:127–32. doi: 10.1002/bjs.7712
10. Hajibandeh S, Hajibandeh S, Maw A. Meta-Analysis and Trial Sequential Analysis of Randomized Controlled Trials Comparing High and Low Ligation of the Inferior Mesenteric Artery in Rectal Cancer Surgery. *Dis Colon Rectum* (2020) 63:988–99. doi: 10.1097/DCR.0000000000001693
11. Sekimoto M, Takemasa I, Mizushima T, Ikeda M, Yamamoto H, Doki Y, et al. Laparoscopic Lymph Node Dissection Around the Inferior Mesenteric Artery With Preservation of the Left Colic Artery. *Surg Endosc* (2011) 25:861–6. doi: 10.1007/s00464-010-1284-7
12. Moszkowicz D, Alsaid B, Bessede T, Penna C, Nordlinger B, Benoît G, et al. Where Does Pelvic Nerve Injury Occur During Rectal Surgery for Cancer? *Colorectal Dis* (2011) 13:1326–34. doi: 10.1111/j.1463-1318.2010.02384.x
13. Açar HI, Kuzu MA. Important Points for Protection of the Autonomic Nerves During Total Mesorectal Excision. *Dis Colon Rectum* (2012) 55:907–12. doi: 10.1097/DCR.0b013e318259b44f
14. Liang JT, Lai HS, Lee PH, Chang KJ. Laparoscopic Pelvic Autonomic Nerve-Preserving Surgery for Sigmoid Colon Cancer. *Ann Surg Oncol* (2008) 15:1609–16. doi: 10.1245/s10434-008-9861-x
15. Nano M, Dal Corso H, Ferronato M, Solej M, Hornung JP, Dei PM. Ligation of the Inferior Mesenteric Artery in the Surgery of Rectal Cancer: Anatomical Considerations. *Dig Surg* (2004) 21:123–6; discussion 126-7. doi: 10.1159/000077347
16. Zhang C, Li GX, Ding ZH, Wu T, Zhong SZ. Preservation of the Autonomic Nerve in Rectal Cancer Surgery: Anatomical Factors in Ligation of the Inferior Mesenteric Artery. *Nan Fang Yi Ke Da Xue Xue Bao* (2006) 26:49–52.
17. Yang XF, Li GX, Luo GH, Zhong SZ, Ding ZH. New Insights Into Autonomic Nerve Preservation in High Ligation of the Inferior Mesenteric Artery in Laparoscopic Surgery for Colorectal Cancer. *Asian Pac J Cancer Prev* (2014) 15:2533–9. doi: 10.7314/apjcp.2014.15.6.2533
18. Kovanov VV, Anikina TI, Rasulova T. Fascial-Cellular Sheath of the Superior Mesenteric Artery and Its Branches. *Arkh Anat Gistol Embriol* (1977) 72:52–8.
19. Sakamoto W, Yamada L, Suzuki O, Kikuchi T, Okayama H, Endo H, et al. Microanatomy of Inferior Mesenteric Artery Sheath in Colorectal Cancer Surgery. *J Anus Rectum Colon* (2019) 3:167–74. doi: 10.23922/jarc.2019-016
20. Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The International Index of Erectile Function (IIEF): A Multidimensional Scale for Assessment of Erectile Dysfunction. *Urology* (1997) 49:822–30. doi: 10.1016/s0090-4295(97)00238-0
21. Heald RJ, Moran BJ, Ryall RD, Sexton R, MacFarlane JK. Rectal Cancer: The Basingstoke Experience of Total Mesorectal Excision, 1978-1997. *Arch Surg* (1998) 133:894–9. doi: 10.1001/archsurg.133.8.894
22. Fukunaga Y, Higashino M, Tanimura S, Kishida S, Fujiwara Y, Ogata A, et al. Laparoscopic Mesorectal Excision With Preservation of the Pelvic Autonomic Nerves for Rectal Cancer. *Hepatogastroenterology* (2007) 54:85–90.
23. Mari GM, Crippa J, Cocozza E, Berselli M, Livraghi L, Carzaniga P, et al. Low Ligation of Inferior Mesenteric Artery in Laparoscopic Anterior Resection for Rectal Cancer Reduces Genitourinary Dysfunction: Results From a Randomized Controlled Trial (Highlow Trial). *Ann Surg* (2019) 269:1018–24. doi: 10.1097/SLA.0000000000002947
24. Wang XJ, Chi P, Lin HM, Lu XR, Huang Y, Xu ZB, et al. A Scoring System to Predict Inferior Mesenteric Artery Lymph Node Metastasis and Prognostic Value of Its Involvement in Rectal Cancer. *Int J Colorectal Dis* (2014) 29:293–300. doi: 10.1007/s00384-013-1816-4
25. Kang J, Hur H, Min BS, Kim NK, Lee KY. Prognostic Impact of Inferior Mesenteric Artery Lymph Node Metastasis in Colorectal Cancer. *Ann Surg Oncol* (2011) 18:704–10. doi: 10.1245/s10434-010-1291-x
26. Kanemitsu Y, Hirai T, Komori K, Kato T. Survival Benefit of High Ligation of the Inferior Mesenteric Artery in Sigmoid Colon or Rectal Cancer Surgery. *Br J Surg* (2006) 93:609–15. doi: 10.1002/bjs.5327
27. Watanabe T, Muro K, Ajioka Y, Hashiguchi Y, Ito Y, Saito Y, et al. Japanese Society for Cancer of the Colon and Rectum (JSCCR) Guidelines 2016 for the Treatment of Colorectal Cancer. *Int J Clin Oncol* (2018) 23:1–34. doi: 10.1007/s10147-017-1101-6
28. Vogel JD, Eskicioglu C, Weiser MR, Feingold DL, Steele SR. The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Treatment of Colon Cancer. *Dis Colon Rectum* (2017) 60:999–1017. doi: 10.1097/DCR.0000000000000926

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Oncology

SYSTEMATIC REVIEW
published: 11 August 2021
doi: 10.3389/fonc.2021.699200

Impact of Surgical Approach on Surgical Resection Quality in Mid- and Low Rectal Cancer, A Bayesian Network Meta-Analysis

Xiaojie Wang[1†], Zhifang Zheng[1†], Qian Yu[2†], Waleed M. Ghareeb[1], Xingrong Lu[1], Ying Huang[1*], Shenghui Huang[1], Shuangming Lin[3*] and Pan Chi[1*]*

[1] Department of Colorectal Surgery, Union Hospital, Fujian Medical University, Fuzhou, China, [2] Department of Pathology, Union Hospital, Fujian Medical University, Fuzhou, China, [3] Department of Gastrointestinal and Anal Surgery, Longyan First Hospital, Affiliated to Fujian Medical University, Longyan, China

OPEN ACCESS

Edited by:
Ren Zhao,
Shanghai Jiao Tong University, China

Reviewed by:
Giulio Aniello Santoro,
Ospedale di Treviso, Italy
Marco Massani,
ULSS2 Marca Trevigiana, Italy

****Correspondence:***
Pan Chi
chipan363@163.com
Ying Huang
hy9033sy@sina.com
Xiaojie Wang
xjwang363@163.com
Shuangming Lin
linsm22@126.com

†These authors have contributed equally to this work

Specialty section:
This article was submitted to Surgical Oncology, a section of the journal Frontiers in Oncology

Received: *23 April 2021*
Accepted: *15 July 2021*
Published: *11 August 2021*

Citation:
Wang X, Zheng Z, Yu Q, Ghareeb WM, Lu X, Huang Y, Huang S, Lin S and Chi P (2021) Impact of Surgical Approach on Surgical Resection Quality in Mid- and Low Rectal Cancer, A Bayesian Network Meta-Analysis. Front. Oncol. 11:699200. doi: 10.3389/fonc.2021.699200

Aim: To evaluate the evidence concerning the quality of surgical resection in laparoscopic (LapTME), robotic (RobTME) and transanal (TaTME) total mesorectal excision for mid-/low rectal cancer.

Methods: A systematic literature search of the PubMed, EMBASE and Cochrane Central Register of Controlled Trials databases was performed. A Bayesian network meta-analysis was utilized to compare surgical resection involved in these 3 surgical techniques by using ADDIS software. Rates of positive circumferential resection margins (CRMs) were the primary endpoint.

Results: A total of 34 articles, 2 randomized clinical trials (RCTs) and 32 non-RCTs, were included in this meta-analysis. Pooled data showed CRM positivity in 114 of 1763 LapTME procedures (6.5%), 54 of 1051 RobTME procedures (5.1%) and 60 of 1276 TaTME procedures (4.7%). There was no statistically significant difference among these 3 surgical approaches in terms of CRM involvement rates and all other surgical resection quality outcomes. The incomplete mesorectal excision rates were 9.6% (69/720) in the LapTME group, 1.9% (11/584) in the RobTME group and 5.6% (45/797) in the TaTME group. Pooled network analysis observed a higher but not statistically significant risk of incomplete mesorectum when comparing both LapTME with RobTME (OR = 1.99; 95% CI = 0.48-11.17) and LapTME with TaTME (OR = 1.90; 95% CI = 0.99-5.25). By comparison, RobTME was most likely to be ranked the best or second best in terms of CRM involvement, complete mesorectal excision, rate of distal resection margin (DRM) involvement and length of DRMs. In addition, RobTME achieved a greater mean tumor distance to the CRM than TaTME. It is worth noting that TaTME was most likely to be ranked the worst in terms of CRM involvement for intersphincteric resection of low rectal cancer.

Conclusion: Overall, RobTME was most likely to be ranked the best in terms of the quality of surgical resection for the treatment of mid-/low rectal cancer. TaTME should be performed with caution in the treatment of low rectal cancer.

Keywords: robotic, transanal, laparoscopic, rectal cancer, quality of surgical resection

INTRODUCTION

Total mesorectal excision (TME) remains the leading surgical approach in the treatment of patients with mid- and low rectal cancer (1). The feasibility of laparoscopic TME (LapTME) has been assessed in several studies and has been widely practiced as an alternative to open surgery in the treatment of mid-/low rectal cancer. This procedure has been found to be oncologically safe and associated with minimally invasive advantages, such as less pain, a shorter hospitalization time, and faster bowel function return (2). However, achieving high-quality TME dissection still might be technically demanding even by experts, especially for tumors in the lower two-thirds of the rectum or for bulky tumors in a narrow, irradiated deep pelvis during laparoscopic operations. The innate limitations associated with laparoscopic TME include the use of rigid instruments, the limited range of motion, the loss of dexterity, fixed trocar positions and the limited view in the narrow, deep pelvic cavity. Two randomized studies [ALaCaRT trial (3) and ACOSOG Z6051 trial (4)] on laparoscopic and open surgeries for the treatment of rectal cancer raised concerns regarding the quality of oncological resection, highlighting the risk of positive circumferential resection margins (CRMs) and incomplete mesorectal excision.

The introduction of two other minimally invasive surgical approaches, robotic (RobTME) and transanal total mesorectal excision (TaTME), for mid-/low rectal cancer surgical treatment has appeared to overcome some of the technical difficulties of laparoscopy (5, 6). The robotic system provides greater maneuverability by enabling surgeons to control wrist motion during the use of endoscopic instruments with high-definition three-dimensional steady vision. The transanal approach to TME was also developed with the aim of improving distal mesorectal dissection, which is the most technically challenging part of transabdominal LapTME, by improving visibility and access to the dissection planes deep in the lower pelvic cavity.

To date, two network meta-analyses comparing these 3 surgical techniques in rectal cancer have been published (7, 8). However, the results were conflicting in terms of the quality of surgical resection, which was measured using CRMs, mesorectal quality, and distal resection margins (DRMs) (9, 10). The first network meta-analysis performed by Simillis et al. (7) demonstrated a decreased rate of positive CRMs in TaTME compared to LapTME, which was in contrast with the results of the second network meta-analysis by Rausa et al. (8) To our knowledge, no prior studies have compared the quality of surgical resection of these three surgical approaches for mid-/low rectal cancer treatment. Therefore, we performed an updated network meta-analysis of the latest and most convincing evidence to evaluate the quality of surgical resection of these 3 minimally invasive surgical techniques for mid-/low rectal cancer.

MATERIALS AND METHODS

Data Sources and Searches

The present study was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines (11). A systematic literature search of the PubMed, EMBASE and Cochrane Central Register of Controlled Trials databases was performed up to June 2019. The ClinicalTrials.gov registry (https://clinicaltrials.gov/) was also considered. Specific research equations were formulated for each database using the following search terms: rectal cancer, rectal carcinoma, surgery, total mesorectal excision, laparoscopy, laparoscopic surgery, transanal total mesorectal excision, TaTME, and robotic surgery. Moreover, the references cited in relevant review articles were cross-checked to identify additional studies.

Inclusion and Exclusion Criteria

We evaluated the checked studies against the following criteria:

1. Population: patients with mid-/low rectal cancer.
2. Intervention: TME.
3. Comparator: at least two of the methods for the treatment of mid-/low rectal cancer (LapTME, RobTME, and TaTME) were compared.
4. Outcome measure: pathological outcomes.
5. Study design: randomized clinical trials (RCTs) or nonrandomized comparative studies (non-RCTs).

All reviews, comments, case reports, and expert opinions were excluded. Duplicates were excluded.

Data Extraction and Quality Assessment

The details of the included studies were extracted from the electronic databases independently by two investigators. Disagreements were resolved by joint review of the studies to reach consensus. The following data were obtained: characteristics of the studies, such as first author name, publication year, study time, surgical treatments, and number of each intervention; demographic characteristics of the participants; and details of the pathological outcomes, including CRM involvement, tumor distance to the CRM, length of DRMs, positive DRMs, mesorectal quality (complete, near complete and incomplete mesorectum), and harvested lymph nodes. The quality of the studies included in this systematic review was assessed independently by the same reviewers with Jadad scores (12) for RCTs and the Newcastle-Ottawa Scale (NOS) (13) for nonrandomized comparative studies.

Outcomes

The rate of positive CRMs was the primary endpoint, and tumor distance to the CRM, length of DRMs, positive DRM rate, mesorectal quality (complete, near complete and incomplete mesorectum) and harvested lymph nodes were the secondary endpoints. A positive CRM was defined when the tumor was located 1 mm or less from the CRM (14). The quality of mesorectal excision was evaluated using the Quirke classification (9). Specifically, a complete mesorectum was defined as an intact mesorectum with only minor irregularities of a smooth mesorectal surface. No defect is deeper than 5 mm. Nearly complete mesorectum was defined as moderate bulk to the mesorectum, but at no site is the muscularis propria visible. Incomplete mesorectum was defined as little bulk to mesorectum with defects down onto muscularis propria (9).

Statistical Analysis

We calculated the odds ratio (OR) and weighted mean difference (WMD) with a 95% confidence interval (CI) for dichotomous and continuous variables. If studies only reported median values or range values, the original data were transformed into forms suitable for meta-analysis using the algorithms proposed by Hozo et al. (15) We performed the multi-treatment network meta-analysis within a Bayesian framework with the Markov Chain Monte Carlo simulation. All data were calculated by using the Aggregate Data Drug Information System (ADDIS) v1.0 and STATA (version 15.0; StataCorp, College Station, TX). The parameters for the network meta-analysis in the ADDIS were as follows: the number of chains, 4; tuning iterations, 20,000; simulation iterations, 50,000; thinning interval, 10; inference samples, 10,000; and variance scaling factor, 2.5. The convergence of the model was judged by the potential scale reduction factor (PSRF) (16); a PSRF closer to 1 indicated better convergence.

Traditional pairwise meta-analysis of direct comparisons was performed using STATA. Statistical heterogeneity between studies was assessed with I^2 statistics. Values of I^2 above 25% and lower than 25% were regarded as heterogeneity and no heterogeneity, respectively (17). A random-effects model was used to incorporate direct data into a single comparison if heterogeneity existed (I^2 > 25%). A fixed-effects model was used for variables with I^2 values lower than 25%.

For the closed-loop comparisons, the consistency test between direct comparisons and indirect estimated comparisons was judged using node-splitting analysis. A consistency model was used when the P value >0.05 in the node-splitting analysis; otherwise, the inconsistency model was used (18). Finally, ranking probabilities were calculated for the results of each treatment under different endpoints to provide the basis for alternative selection.

RESULTS

Identification of Studies

The results of the literature search identified 2878 articles for initial screening based on the titles. Among them, 1094 articles were imported for detailed information based on the abstracts. Of these, 58 articles were retrieved for full-text review, and among them, 24 studies were excluded based on the selection criteria. Finally, we included 34 relevant articles that were reviewed for meta-analysis (5, 6, 19–50). There were 2 RCTs and 32 nRCTs. A flow chart for the literature search and study selection is shown in **Figure 1**.

Characteristics of the Included Studies

The characteristics of the included studies are summarized in **Table 1**. Of the included studies, 26 of 32 (80%) non-RCTs were of high quality (NOS score ≥ 7), and the other 2 RCTs were of medium quality (Jadad score = 3). In total, 4429 patients with mid-/low rectal cancer were included in the study: 1856 patients in the LapTME group, 1211 patients in the RobTME group, and 1362 patients in the TaTME group. Among them, there were more male (68.1%) than female patients (31.9%). The mean age varied from 54 to 70 years, and the mean body mass index (BMI) ranged from 21.4 kg/m^2 to 29.0 kg/m^2. The mean tumor distance from anal verge varied from 1.5 to 8.0 cm. Studies by JS Park et al. (24), Kuo et al. (21), SY Park et al. (20) and Kanso et al. (30) included only low rectal cancer patients who underwent intersphincteric resection (ISR). The connection between each surgical approach was analyzed, and each square reflecting the surgical approach and two squares linked together by an edge showed the number of studies comparing the two corresponding surgical techniques directly (**Figure 2**).

Definition of Mid-/Low Rectal Cancer

The most commonly used definition of mid-/low rectal cancer was the rectal adenocarcinomas with the inferior margins located within 10 cm of the anal verge. The second commonly used definition was the tumor located within 12 cm of the anal verge. For the definition of low rectal cancer, 4 studies defined low rectal cancer as a tumor located within 5 cm of the anal verge, while 2 studies defined low rectal cancer as a tumor located up to 6 cm from the anal verge. In addition to the commonly used anatomical marker of anal verge, two studies by Chouillard (36) and Velthuis (23) used the dentate line as a measuring mark to define tumor distance. Rigid proctoscopy/sigmoidoscopy was the technique most commonly used to measure the tumor distance, while Persiani et al. (48) used MRI to evaluate the distance between the distal end of the tumor and the anorectal junction (**Table 2**).

Neoadjuvant Treatment

The prevalence of patients who underwent neoadjuvant treatment varied from 16% to 100%. Concomitant radiochemotherapy was employed by the studies examined in this review, except Chen et al. (45) who did not clearly specify whether neoadjuvant chemotherapy or concomitant radiochemotherapy were adopted. Only a small number of patients received chemotherapy alone [1 patients in Roodbeen research (49) and 32 cases in Bedirli research (32)]. Induction therapy was not reported in included studies. Although the exact nature of neoadjuvant radiotherapy differed between the included studies, the majority of studies administered long-course preoperative radiochemotherapy (45 to 50.4 Gy

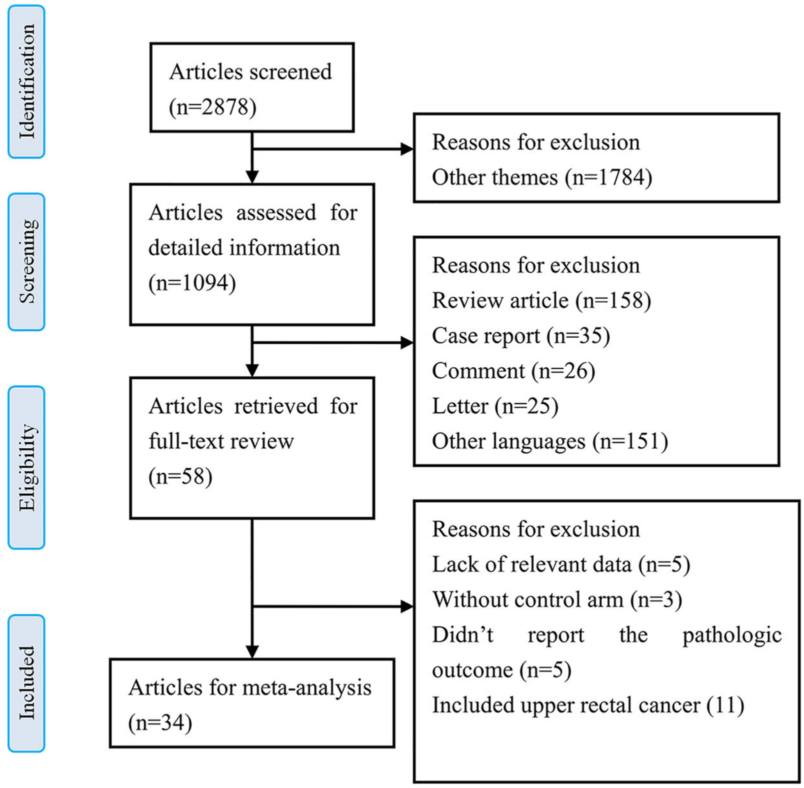


FIGURE 1 | Flow chart for the literature search and study selection.

delivered over a period of 5 to 6 weeks). Rasulov et al. (39) reported the use of long-course radiochemotherapy for T3-T4 low rectal cancer, while for other patients short-course preoperative radiochemotherapy (25 Gy) were offered. Serin et al. (25) employed short-course radiotherapy (25 Gy) for patients without risk of lateral margin positivity. Velthuis et al. (23) also reported the use of 25 Gy pelvic irradiation for low risk patients of T2-3N0-1 tumor (**Table 3**).

Primary Outcomes

The results of traditional pairwise meta-analysis and network meta-analysis are displayed in **Tables 4** and **5**, respectively. Thirty-two studies reported the rate of CRM involvement. Two of them were excluded due to different CRM definitions. Velthuis et al. (23) and Yoo et al. (26) defined CRM involvement as when the tumor was located 2 mm or less from the CRM, which might overestimate the CRM positive rate. Finally, 30 studies were included, reporting 4090 patients. Pooled data showed CRM positivity in 114 of 1763 LapTME procedures (6.5%), 54 of 1051 RobTME procedures (5.1%) and 60 of 1276 TaTME procedures (4.7%). According to the consistency test, the consistency model was used to pool the data on positive CRM rates (all the P values > 0.05 in node-splitting analysis). In addition, when the PSRFs ranged from 1.00 to 1.01, good convergence of the model was obtained. Network analysis showed that there was no significant difference among these 3 surgical approaches. The rank plot illustrating the empirical probabilities for each pathological outcome in each surgical approach ranked first through third is depicted in **Figure 3**. The transanal approach had a high probability of being the best treatment, considering that it had the lowest CRM involvement rate. The results from traditional direct pairwise meta-analysis demonstrated no significant difference regarding the CRM involvement rates between LapTME and RobTME (OR=1.312, 95% CI 0.805-2.136, P=0.275) or between LapTME and TaTME (OR=1.476, 95% CI 0.987-2.209, P=0.058). However, subgroup analysis for comparison of the positive CRM rate among types of ISR showed contrasting results. The pooled CRM involvement rate was 9.8% in the TaTME group, which was slightly higher than the rate of 9.0% in the LapTME group and 8.8% in the RobTME group, although this trend did not reach statistical significance. The RobTME group had the highest probability of being the best surgical treatment to obtain free CRMs for low rectal cancer, whereas TaTME ranked the worst.

Secondary Outcomes

Nineteen studies reported the mesorectal quality. The consistency test showed good consistency between direct comparisons and indirect estimated comparisons (all the P values > 0.05 in node-splitting analysis), and good convergence

TABLE 1 | Characteristics of included studies.

Study	Year	Study year	Study design	Group			Gender (male, %)			Mean age			Mean BMI			Tumor distance from anal verge (cm)			CRT (n, %)			Quality score&
				Lap	Rob	Ta	Lap	Rob	Ta	Lap	Rob	Ta	Lap	Rob	Ta	Lap	Rob	Ta	Lap	Rob	Ta	
Bianchi (5)	2010	2008-2009	Non-RCT	25	25		17 (68%)	18 (72%)		62.0	69.0		26.5	24.6		NA	NA		10 (40%)	13 (52%)		7
Baek (19)	2013	2007-2010	Non-RCT	37	47		28 (76%)	31 (66%)		61.8	58.0		23.4	23.4		5.5	4.4		12 (32%)	20 (43%)		9
SY Park (20)	2013	2008-2011	Non-RCT	40	40		25 (63%)	28 (70%)		63.6	57.3		24.3	23.9		3.6	3.4		20 (50%)	32 (80%)		6
Kuo (21)	2014	2009-2013	Non-RCT	28	36		17 (61%)	21 (58%)		54.9	55.9		NA	NA		3.7	3.8		28 (100%)	28 (78%)		6
Denost (22)	2014	2008-2012	RCT	50		50	32 (64%)		37 (74%)	63.0		64.0	25.6		25.1	4.0		4.0	44 (88%)		40 (80%)	3#
Velthuis (23)	2014	2012-2013	Non-RCT	25		25	18 (72%)		18 (72%)	65.0		64.0	25.0		27.0	6.0		8.0	25 (100%)		25 (100%)	9
JS Park (24)	2015	2008-2011	Non-RCT	106	106		71 (67%)	75 (71%)		61.7	59.6		23.8	24.3		3.3	3.2		60 (57%)	68 (64%)		9
Serin (25)	2015	2005-2013	Non-RCT	65	14		65 (100%)	14 (100%)		57.0	54.0		26.0	24.7					65 (100%)	14 (100%)		8
Yoo (26)	2015	2006-2011	Non-RCT	26	44		19 (73%)	35 (80%)		60.5	59.8		21.4	24.1		3.7	3.2		7 (27%)	24 (55%)		6
Chen (27)	2015	2013-2015	Non-RCT	100		50	76 (76%)		38 (76%)	58.3		57.3	24.6		24.2	6.7		5.8	100 (100%)		50 (100%)	7
De'Angelis (28)	2015	2008-2014	Non-RCT	32		32	21 (66%)		21 (66%)	67.1		64.9	24.5		25.1	3.7		4.0	23 (72%)		27 (84%)	9
Fernandez-Hevia (29)	2015	2011-2013	Non-RCT	37		37	22 (59%)		24 (65%)	69.5		64.5	25.1		23.7	NA		NA	21 (57%)		27 (73%)	8
Kanso (30)	2015	2005-2013	Non-RCT	34		51	26 (76%)		36 (71%)	59.0		59.0	24.0		24.0	1.8		1.6	28 (82%)		43 (84%)	9
Perdawood (31)	2015	2013-2015	Non-RCT	25		25	19 (76%)		19 (76%)	70.0		70.0	26.0		28.0	8.0		8.0	4 (16%)		7 (28%)	8
Bedirli (32)	2016	2013-2015	Non-RCT	28	35		19 (68%)	24 (69%)		60.4	64.7		23.2	24.7		NA	NA		28 (100%)	35 (100%)		8
Feroci (33)	2016	2004-2014	Non-RCT	58	53		42 (72%)	27 (51%)		66.0	66.0		24.6	24.6		8.0	8.0		25 (43%)	26 (49%)		6
Law (34)	2016	2008-2015	Non-RCT	171	220		97 (57%)	148 (67%)		67.0	65.0		24.6	24.9		8.0	7.0		50 (29%)	91 (41%)		6
Lim (35)	2016	2006-2010	Non-RCT	64	74		46 (72%)	50 (68%)		65.8	65.1		22.7	23.4		6.7	5.3		64 (100%)	74 (100%)		9
Chouillard (36)	2016	2011-2014	Non-RCT	15		18	7 (47%)		6 (33%)	57.8		55.4	29.0		27.1	NA		NA	12 (80%)		14 (78%)	8
Lelong (37)	2016	2008-2013	Non-RCT	38		34	22 (58%)		23 (68%)				24.2		24.0				35 (92%)		30 (88%)	9
Marks (38)	2016	2012-2014	Non-RCT	17		17	NA		NA	60.0		59.0	25.9		26.4	NA		NA	NA		NA	8
Rasulov (39)	2016	2013-2016	Non-RCT	23		22	14 (61%)		11 (50%)	60.0		56.0	26.0		26.0	7.0		6.5	19 (83%)		19 (86%)	7
Kim (40)	2017	2012-2015	RCT	73	66		52 (63%)	51 (61%)		59.7	60.4		23.6	24.1		NA	NA		58 (79%)	51 (77%)		3#
Perez (41)	2017	2013-2016	Non-RCT		60	55		44 (73%)	40 (73%)		NA	NA		25.8	24.9		NA	NA		42 (70%)	35 (64%)	8
Chang (6)	2017	2014-2017	Non-RCT	23		23	13 (57%)		13 (57%)	62.9		62.4	25.0		25.8	5.9		4.3	14 (61%)		8 (35%)	9
Perdawood2 (42)	2017	2015-2017	Non-RCT	100		100	69 (69%)		72 (72%)	66.9		67.3	25.4		25.7	7.8		7.5	27 (27%)		18 (18%)	8
Lee (43)	2018	2011-2017	Non-RCT		370	226		235 (64%)	142 (63%)		62.5	62.1		25.8	26.1		5.6	5.6		256 (69%)	160 (71%)	9
Seow-En (44)	2018	2012-2015	Non-RCT		21	6		14 (67%)	3 (50%)		NA	NA		24.0	24.0		5.0	7.0		7 (33%)	2 (33%)	9
Mege (47)	2018	2014-2017	Non-RCT	34		34	23 (68%)		23 (68%)	59.0		58.0	25.0		25.0	2.2*		1.3*	29 (85%)		29 (85%)	9
Persiani (48)	2018	2007-2017	Non-RCT	46		46	31 (67%)		30 (65%)	66.5		69.0	25.6		25.0	6.0		5.0	43 (93%)		26 (57%)	6
Roodbeen (49)	2018	2006-2017	Non-RCT	41		41	32 (78%)		34 (83%)	66.0		62.5	26.1		26.7	1.5		2.0	18 (44%)		16 (39%)	9
Rubinkiewicz (50)	2018	2012-2018	Non-RCT	35		35	24 (69%)		24 (69%)	60.3		64.3	27.1		26.1	3.2		2.9	31 (89%)		31 (89%)	8
Chen2 (45)	2019	2008-2018	Non-RCT	64		39	42 (66%)		29 (74%)	64.0		62.0	24.6		25.4	5.8		4.3	31 (48%)		15 (38%)	7
Detering (46)	2019	2015-2017	Non-RCT	396		396	281 (71%)		288 (73%)	NA		NA	NA		NA	NA		NA	156 (39%)		135 (34%)	8

**Distance to external sphincter; &Evaluated by Newcastle-Ottawa Scale; #Evaluated by Jadad score; BMI, body mass index; NA, not available.*

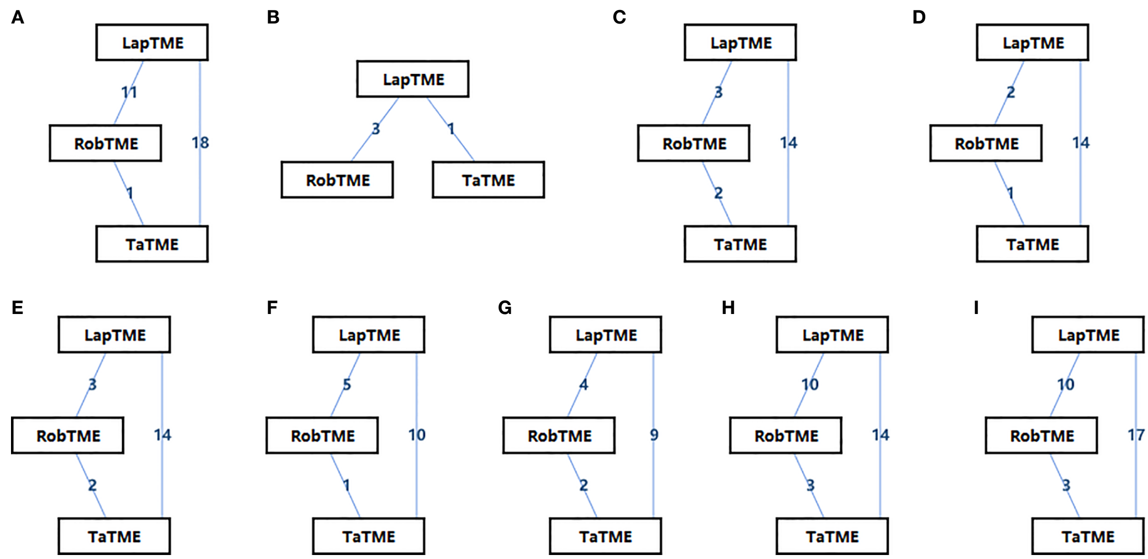


FIGURE 2 | Network diagrams of the eligible studies. **(A)** CRM involvement; **(B)** CRM involvement for ISR; **(C)** Complete mesorectum; **(D)** Near complete mesorectum; **(E)** Incomplete mesorectum; **(F)** DRM involvement; **(G)** Tumor distance to the CRM; **(H)** DRM distance; **(I)** Harvested lymph nodes.

TABLE 2 | Definition of mid-/low rectal cancer in included studies.

Study	Year	Definition of mid- and low rectal cancer
Bianchi (5)	2010	≤ 12 cm from the anal verge
Baek (19)	2013	NR
SY Park (20)	2013	NR
Kuo (21)	2014	NR
Denost (22)	2014	Low rectal cancer: < 6 cm from the anal verge
Velthuis (23)	2014	Low rectal cancer: 0-5 cm from the dentate line; mid rectal cancer: 5-10 cm from the dentate line
JS Park (24)	2015	Low rectal cancer: ≤ 4 cm of the anal verge
Serin (25)	2015	≤10 cm from the anal verge, measured by rigid sigmoidoscope
Yoo (26)	2015	≤ 5 cm from the anal verge, measured by digital rectal examination and/or rigid sigmoidoscopy
Chen (27)	2015	NR
De'Angelis (28)	2015	Low rectal cancer: ≤ 5 cm from the anal verge
Fernandez-Hevia (29)	2015	≤ 10 cm from the anal verge
Kanso (30)	2015	NR
Perdawood (31)	2015	≤ 10 cm from the anal verge, measured by rigid proctoscopy
Bedirli (32)	2016	Middle and lower 2/3 of rectum
Feroci (33)	2016	≤ 12 cm from the anal verge
Law (34)	2016	≤ 12 cm from the anal verge
Lim (35)	2016	≤ 12 cm from the anal verge
Chouillard (36)	2016	≤ 7 cm from the dentate line
Lelong (37)	2016	NR
Marks (38)	2016	NR
Rasulov (39)	2016	≤ 10 cm from the anal verge, measured by rigid rectoscopy
Kim (40)	2017	≤ 9 cm from the anal verge
Perez (41)	2017	Low rectal cancer: < 6cm from anal verge; mid rectal cancer: 6-12cm from anal verge
Chang (6)	2017	Low rectal cancer: ≤ 7 cm from the anal verge
Perdawood2 (42)	2017	NR
Lee (43)	2018	≤ 10 cm from the anal verge
Seow-En (44)	2018	NR
Mege (47)	2018	NR
Persiani (48)	2018	Low rectal cancer: 0–5 cm; mid rectal cancer: 5.1–10 cm, measured by MRI
Roodbeen (49)	2018	Low rectal cancer: tumor distal border was located distal to the point where the levator ani muscles insert on the pelvic bone on sagittal MRI
Rubinkiewicz (50)	2018	Low rectal cancer: <5 cm from the anal verge
Chen2 (45)	2019	≤ 7 cm from the anal verge
Detering (46)	2019	≤ 10 cm from the anal verge

TABLE 3 | Neoadjuvant treatment schedules in included studies.

Study	Year	Indication for neoadjuvant treatment	Neoadjuvant schedule			
			Received radiotherapy (yes/no)	Radiotherapy schedule	Received chemotherapy (yes/no)	Chemotherapy schedule
Bianchi (5)	2010	Tumor spread to the mesorectum, or N1-2 by MRI or endoscopic ultrasound	Yes	45 Gy in 5 fractions	Yes	Capecitabine
Baek (19)	2013	NR	Yes	50.4Gy, 45 Gy/25 fractions followed by a 5.4Gy boost	Yes	5-FU
SY Park (20)	2013	T3, T4, or N+	Yes	50 Gy in 25 fractions for 5 weeks	Yes	NR
Kuo (21)	2014	T3, T4, or N+	Yes	NR	Yes	NR
Denost (22)	2014	T3, T4, or N+	Yes	45 Gy in 5 weeks	Yes	5-FU and Capecitabine
Velthuis (23)	2014	T2-3N0-1 or T2-3N2	Yes	T2-3N0-1: 25 Gy in 5 fractions, T2-3N2: 50 Gy in 25 fractions	Yes	5-FU
JS Park (24)	2015	NR	Yes	50 Gy in 25 fractions for 5 weeks	Yes	NR
Serin (25)	2015	T3, T4, or N+	Yes	45–50.4 Gy; short-course radiotherapy (25 Gy pelvic irradiation) for patients without risk of lateral margin positivity	Yes	5-FU and leucoverin
Yoo (26)	2015	CRM+ or lymph nodes that escaped the TME plane	Yes	50.8 Gy in 28 fractions	Yes	5-FU based chemotherapy
Chen (27)	2015	Stage II or III	Yes	50.4Gy, 45 Gy/25 fractions followed by a 5.4Gy boost	Yes	oral 5-FU
De'Angelis (28)	2015	T3, T4N0, or T1-T4N1-N2	Yes	45–50.4 Gy delivered in daily fractions of 1.8-2 Gy for 5-6 weeks	Yes	5-FU infusion
Fernandez-Hevia (29)	2015	T3, T4N0, or T1-T4N1-N2	Yes	45 Gy/25 fractions	Yes	5-FU infusion
Kanso (30)	2015	T3, T4, or N+	Yes	50 Gy in 5 weeks	Yes	NR
Perdawood (31)	2015	T3 (≤ 5 mm from the tumor to the mesorectal fascia), T4	Yes	50.4 Gy in 28 fractions	Yes	5-FU
Bedirli (32)	2016	NR	Yes	NR	Yes, 19(54%) in Rob group and 13 (46%) in Lap group only had neoadjuvant chemotherapy	NR
Feroci (33)	2016	T3, T4, or N+	Yes	NR	Yes	NR
Law (34)	2016	mesorectal margin was at risk (≤ 1 mm by MRI)	Yes	45–54 Gy	Yes	NR
Lim (35)	2016	T3, T4, or N+	Yes	50.4 Gy	Yes	5-FU
Chouillard (36)	2016	higher than T2, or N+	Yes	45-50 Gy in 5-6 weeks	Yes	5-FU
Lelong (37)	2016	T3, T4, or N+, or some T2 ultralow tumors	Yes	45-50 Gy in 25 fractions	Yes	Capecitabine
Marks (38)	2016	NR	Yes	NR	Yes	NR
Rasulov (39)	2016	mrT3abN0-1 tumors located 5-10 cm from the anal verge or T2N0-1 tumors located <5 cm from the anal verge did not receive neoadjuvant therapy	Yes	T3-T4 low rectal cancer: 50 Gy in 25 fractions; others: 25 Gy in 5 fractions	Yes	Oral capecitabine
Kim (40)	2017	T3, T4, or N+	Yes	50.4 Gy	Yes	5-FU based chemotherapy
Perez (41)	2017	NR	Yes	NR	Yes	NR
Chang (6)	2017	T0-3 N0-1	Yes	NR	Yes	NR
Perdawood2 (42)	2017	T3 (tumor at 5-10 cm from the anal verge, < 5 mm from the deepest tumor invasion to the mesorectal fascia; below 5 cm from the anal verge: all) or T4	Yes	50.8 Gy in 28 fractions	Yes	5-FU based or equivalent chemotherapy
Lee (43)	2018	T3, T4, or N+	Yes	Long course chemoradiation	Yes	NR
Seow-En (44)	2018	NR	Yes	NR	Yes	NR

(Continued)

TABLE 3 | Continued

Study	Year	Indication for neoadjuvant treatment	Neoadjuvant schedule			
			Received radiotherapy (yes/no)	Radiotherapy schedule	Received chemotherapy (yes/no)	Chemotherapy schedule
Mege (47)	2018	T3, T4, or N+	Yes	50 Gy in 5 weeks	Yes	NR
Persiani (48)	2018	T3, T4, or N+	Yes	NR	Yes	NR
Roodbeen (49)	2018	NR, decided by multidisciplinary team	Yes	Long course chemoradiation	Yes, 1 patients in TaTME group received only chemotherapy	NR
Rubinkiewicz (50)	2018	T3, T4, or N+	Yes	50.4 Gy	Yes	NR
Chen2 (45)	2019	NR	NR	NR	NR	NR
Detering (46)	2019	NR	Yes	NR, including Short Course Radiotherapy-Immediate Surgery, Short Course Radiotherapy-Delayed Surgery, and Long Course Radiotherapy/Chemoradiotherapy	NR	NR

TaTME, transanal total mesorectal excision; NR, not reported.

of the model was obtained (all PSRFs ranged from 1.00 to 1.01) for all mesorectal quality outcomes. Complete mesorectal excision was observed in 541 (75.1%) of 720 patients who underwent LapTME, in 547 (93.7%) of 584 patients who underwent RobTME and in 647 (81.2%) of 797 patients who underwent TaTME. The network analysis results showed no significant difference in the complete mesorectal excision rates among these 3 surgical approaches. The results from traditional direct pairwise meta-analysis demonstrated no significant difference for complete mesorectal excision between LapTME and RobTME (OR=0.868, 95% CI 0.411-1.831, P=0.709), between RobTME and TaTME (OR=1.413, 95% CI 0.543-3.675, P=0.479), or between LapTME and TaTME (OR=0.735, 95% CI 0.452-1.197, P=0.216). In addition, RobTME ranked best with the highest probability for complete mesorectal excision.

The incomplete mesorectal excision rates were 9.6% (69/720) in the LapTME group, 1.9% (11/584) in the RobTME group and 5.6% (45/797) in the TaTME group. Pooled network analysis observed a higher but not statistically significant risk of incomplete mesorectum when comparing both LapTME with RobTME (OR = 1.99; 95% CI = 0.48-11.17) and LapTME with TaTME (OR = 1.90; 95% CI = 0.99-5.25). According to the results of direct pairwise meta-analysis, there was no significant difference between LapTME and RobTME (OR=1.612, 95% CI 0.065-39.911, P=0.770), RobTME and TaTME (OR=1.180, 95% CI 0.432-3.223, P=0.747), or LapTME and TaTME (OR=1.531, 95% CI 0.998-2.351, P=0.051). Moreover, LapTME ranked the worst for obtaining incomplete mesorectal excision. Compared with TaTME, RobTME achieved a greater mean tumor distance to the CRM (WMD, 0.987; 95% CI 0.628–1.345; P < 0.001) in both the direct comparison and indirect network estimated comparison (WMD, 4.31; 95% CI 0.38–7.78). The inconsistency model was used because all the P values < 0.05 in node-splitting analysis.

Sixteen studies reported DRMs. The pooled DRM positivity rate was 2.0% (14/706) for the LapTME group, 0.3% (2/739) for the RobTME group and 1.9% (12/638) for the TaTME group. Synthesis of the results found that the DRM positive rate was not affected by the 3 different approaches. Similarly, no differences in the length of DRMs among the 3 surgical approaches were found. No significant difference was discovered between the two groups with respect to the length of DRMs (LapTME *vs* RobTME, WMD = -0.084, 95% CI -0.279-0.111, P = 0.398; RobTME vs TaTME, WMD = 0.570, 95% CI -0.886-2.026, P = 0.443; LapTME vs TaTME, WMD = -0.072, 95% CI -0.333-0.189, P = 0.588). RobTME ranked the best with a high probability for the lowest rate of DRM involvement, the longest length of DRMs, and the number of harvested lymph nodes.

DISCUSSION

Since TME for mid-/low rectal cancer has been elucidated to optimize locoregional clearance (51), the LR rate has decreased to approximately 6% (52), and an optimal surgical approach for mid-/low rectal cancer has yet to be achieved. The quality of

TABLE 4 | Results of traditional pair-wise meta-analysis.

Item	Comparison	I2	Model	SMD/OR (95%CI)			Z	P-value
Involved CRM	LapTME VS RobTME	0	Fixed-effect model	1.312	0.805	2.136	1.09	0.275
	LapTME VS TaTME	14.3	Fixed-effect model	1.476	0.987	2.209	1.90	0.058
Complete mesorectum	LapTME VS RobTME	21.1	Fixed-effect model	0.868	0.411	1.831	0.37	0.709
	RobTME VS TaTME	48.6	Random effects model	1.413	0.543	3.675	0.71	0.479
	LapTME VS TaTME	56.2	Random effects model	0.735	0.452	1.197	1.24	0.216
Near complete mesorectum	LapTME VS RobTME	0	Fixed-effect model	1.070	0.496	2.307	0.17	0.863
	LapTME VS TaTME	1.6	Fixed-effect model	0.806	0.573	1.132	1.24	0.214
Incomplete mesorectum	LapTME VS RobTME	54.8	Random effects model	1.612	0.065	39.911	0.29	0.770
	RobTME VS TaTME	0	Fixed-effect model	1.180	0.432	3.223	0.32	0.747
	LapTME VS TaTME	0	Fixed-effect model	1.531	0.998	2.351	1.95	0.051
Tumor distance to CRM	LapTME VS RobTME	0	Fixed-effect model	0.017	-0.179	0.213	0.17	0.863
	RobTME VS TaTME	0	Fixed-effect model	0.987	0.628	1.345	5.39	0.000
	LapTME VS TaTME	90.9	Random effects model	-0.461	-0.976	0.055	1.75	0.080
Involved DRM	LapTME VS RobTME	0	Fixed-effect model	2.268	0.415	12.389	0.95	0.344
	LapTME VS TaTME	0	Fixed-effect model	1.392	0.616	3.149	0.80	0.426
DRM distance	LapTME VS RobTME	65.8	Random effects model	-0.084	-0.279	0.111	0.84	0.398
	RobTME VS TaTME	97.1	Random effects model	0.570	-0.886	2.026	0.77	0.443
	LapTME VS TaTME	79.2	Random effects model	-0.072	-0.333	0.189	0.54	0.588
Harvested lymph node	LapTME VS RobTME	76.4	Random effects model	-0.090	-0.358	0.178	0.66	0.512
	RobTME VS TaTME	0	Fixed-effect model	0.098	-0.051	0.247	1.29	0.196
	LapTME VS TaTME	45.3	Random effects model	-0.131	-0.283	0.020	1.70	0.090

CRM, circumferential resection margin; LapTME, laparoscopic total mesorectal excision; RobTME, robotic total mesorectal excision; TaTME, transanal total mesorectal excision; ISR, intersphincteric resection; DRM, distal resection margin.

surgical resection metrics for rectal cancer is defined and evaluated by positive CRMs, incomplete planes of mesorectal excision and positive DRMs (53). The relationship between the quality of surgical resection and long-term oncological outcomes has been well established (53), and the quality of surgical resection has been recommended for evaluating novel surgical interventions (54). Compared with previous reports of meta-analyses (7, 8), this study used network meta-analysis to comprehensively estimate the quality of surgical resection in RobTME, TaTME, and LapTME for mid-/low rectal cancer treatment. The results demonstrated that RobTME achieved a greater mean tumor distance to the CRM than TaTME. In addition, no difference was observed in terms of the CRM involvement rates and all other surgical resection quality variables among RobTME, TaTME, and LapTME. By comparison, RobTME was most likely to be ranked the best in terms of CRM involvement, complete mesorectal excision, rate of DRM involvement and length of DRMs. TaTME was most likely to be ranked the worst in terms of CRM involvement for ISR in low rectal cancer.

The CRM was introduced as a powerful prognostic factor for rectal cancer resection and an important index for measuring the curative effect of surgery. Many large-scale studies have been published demonstrating the value of CRM involvement for local recurrence, overall recurrence and cancer-specific mortality (55, 56). Moreover, since cancer metastases have been found to spread to the distal mesorectum in approximately 40% of rectal cancer cases, a potentially residual disease in the distal mesorectum predisposes patients to pelvic recurrence (57). However, tapering of the distal mesorectum makes radical resection of mid- and low rectal lesions difficult with laparoscopy. Previous RCTs found that CRM rates varied from 4.0% to 15.5% with the laparoscopic approach (58, 59), in line with the results of our pooled CRM rate of 6.5%. However, a higher CRM rate of 9.0% in laparoscopic ISR was found in the present study, coinciding with a rate of 9.4% in a previous multicenter study (24). For this reason, TaTME has been developed as an alternative technique for the treatment of mid-/low rectal cancer, as TaTME provides better dissection of the presacral plane and the rectoprostatic plane or rectovaginal plane with better visualization of the distal rectum (60). Although TaTME performed in mid-/low rectal cancer patients has shown encouraging results (61), its oncological feasibility and safety are yet to be verified through ongoing large RCTs (COLOR III), as the results are only expected approximately in the year 2022 (62). Prior traditional systematic reviews by Hu et al. (63) and Wu et al. (64) comparing LapTME to TaTME for mid-/low rectal cancer showed that TaTME was associated with a reduced positive CRM rate and could achieve complete tumor resection with improved long-term survival. Rubinkiewicz et al. (65) conducted an updated meta-analysis to compare the pure standard LapTME and TaTME procedures by excluding studies on abdominoperineal resection or cases of Hartmann resection. No significant differences regarding the CRM, completeness of mesorectal excision, or DRM were found. However, the sample size in the TaTME group in these previous meta-analyses (414 cases in the Hu study, 348 cases in the Wu study, and 358 in the Rubinkiewicz study) was still insufficient, which could have influenced the statistical significance. Investigators of the COLOR III study estimated that at least 732 patients would be required for the TaTME arm to demonstrate a CRM difference based on an estimated CRM rate of 7% (62). The estimated CRM rate in the COLOR III study was quite similar to our current pooled results. However, with a total of 1362 patients included in the TaTME group of the present network meta-analysis, we failed to find a benefit of TaTME in terms of the CRM rate.

TABLE 5 | Results of network meta-analysis.

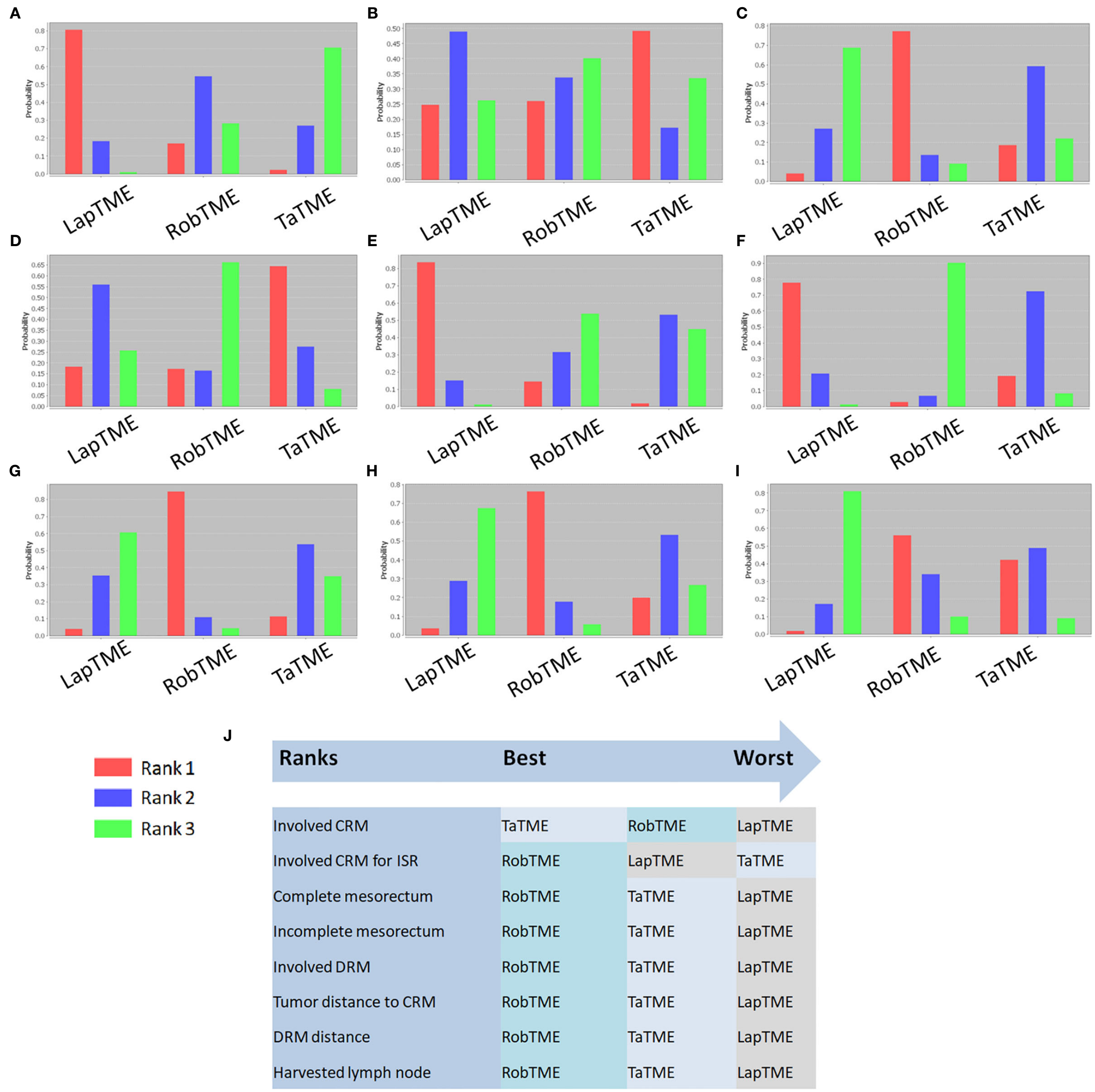
	Compare with LapTME	Compare with RobTME	Compare with TaTME
Involved CRM			
LapTME		1.30 (0.71, 2.35)	1.57 (0.98, 2.73)
RobTME	0.77 (0.43, 1.41)		1.21 (0.61, 2.63)
TaTME	0.64 (0.37, 1.02)	0.83 (0.38, 1.64)	
Involved CRM for ISR			
LapTME		1.07 (0.48, 2.55)	0.86 (0.15, 3.73)
RobTME	0.94 (0.39, 2.10)		0.81 (0.12, 4.61)
TaTME	1.16 (0.27, 6.75)	1.23 (0.22, 8.21)	
Complete mesorectum			
LapTME		0.65 (0.30, 1.35)	0.86 (0.53, 1.30)
RobTME	1.53 (0.74, 3.38)		1.34 (0.60, 2.80)
TaTME	1.16 (0.77, 1.88)	0.75 (0.36, 1.67)	
Near complete mesorectum			
LapTME		1.21 (0.50, 2.78)	0.85 (0.56, 1.36)
RobTME	0.83 (0.36, 1.98)		0.70 (0.31, 1.79)
TaTME	1.17 (0.73, 1.78)	1.42 (0.56, 3.21)	
Incomplete mesorectum			
LapTME		1.99 (0.48, 11.17)	1.90 (0.99, 5.25)
RobTME	0.50 (0.09, 2.07)		0.96 (0.22, 4.43)
TaTME	0.53 (0.19, 1.01)	1.05 (0.23, 4.54)	
Involved DRM			
LapTME		8.75 (0.85, 126.50)	1.71 (0.46, 8.68)
RobTME	0.11 (0.01, 1.17)		0.20 (0.01, 1.98)
TaTME	0.58 (0.12, 2.19)	5.04 (0.50, 76.57)	
Tumor distance to CRM			
LapTME		-1.83 (-4.49, 0.71)	-0.33 (-2.17, 1.63)
RobTME	1.83 (-0.71, 4.49)		1.50 (-1.24, 4.45)
TaTME	0.33 (-1.63, 2.17)	-1.50 (-4.45, 1.24)	
DRM distance			
LapTME		-0.24 (-0.57, 0.10)	-0.08 (-0.39, 0.21)
RobTME	0.24 (-0.10, 0.57)		0.15 (-0.24, 0.54)
TaTME	0.08 (-0.21, 0.39)	-0.15 (-0.54, 0.24)	
Harvested lymph node			
LapTME		-0.96 (-2.62, 0.59)	-0.80 (-2.01, 0.49)
RobTME	0.96 (-0.59, 2.62)		0.17 (-1.59, 2.08)
TaTME	0.80 (-0.49, 2.01)	-0.17 (-2.08, 1.59)	

CRM, circumferential resection margin; LapTME, laparoscopic total mesorectal excision; RobTME, robotic total mesorectal excision; TaTME, transanal total mesorectal excision; ISR, intersphincteric resection; DRM, distal resection margin.

Admittedly, the surgical techniques used in TaTME might not be standardized, and performing TME from below is challenging due to the limited anatomical landmarks.

A robotic-assisted approach, another alternative technique, provides wrist motion for endoscopic instruments to overcome several of the technical difficulties associated with laparoscopy. A lower rate of CRM involvement (OR = 0.5) was found to be associated with RobTME in an early meta-analysis containing 592 patients (324 in the RobTME group and 268 in the LapTME group) (66). However, the early results of a recent RCT (ROLARR trial) showed that CRM involvement rates were comparable between robotic-assisted (5.1%) and conventional laparoscopic (6.3%) rectal cancer resection, in accordance with an updated systematic review following the publication of the ROLARR trial (67) and our current results.

Although little data exist regarding head-to-head comparative analyses of RobTME and TaTME, our Bayesian network meta-analysis allowed us to compare these 3 techniques indirectly and gain more precise effect estimates by collectively evaluating direct and indirect comparisons. Although no difference was observed in terms of CRM involvement among these 3 techniques, RobTME achieved a significantly safer CRM rate than TaTME. In addition, the present study showed that RobTME had a high probability of being the best surgical treatment with regard to CRM involvement in ISR procedures. This was probably due to the ability of the versatile instruments to dissect as far caudally as the intersphincteric space while compensating for the challenges posed by the deep pelvis. Two published network meta-analyses (7, 8) comparing these 3 surgical techniques in rectal cancer came to different conclusions about CRM involvement because of several substantial biases. First, the network meta-analysis by Simillis et al. (7) had seriously different sample sizes among the 4 different surgical techniques compared. Only 50 TaTME cases were included compared to 2350 open, 3276 laparoscopic, and 561 robotic cases, which resulted in very large statistical errors. For instance, the odds ratio for the comparison of conversion rates between TaTME and open TME was as high as 4964, with a large 95% CI (0.6- 39,611,894). Second, it might be considered that all the TaTME studies included in the two previous network meta-analyses included only patients with mid-/low rectal cancers, unlike data from LapTME and RobTME studies that also included upper rectal cancers. CRM involvement rates were



Ranks	Best		Worst
Involved CRM	TaTME	RobTME	LapTME
Involved CRM for ISR	RobTME	LapTME	TaTME
Complete mesorectum	RobTME	TaTME	LapTME
Incomplete mesorectum	RobTME	TaTME	LapTME
Involved DRM	RobTME	TaTME	LapTME
Tumor distance to CRM	RobTME	TaTME	LapTME
DRM distance	RobTME	TaTME	LapTME
Harvested lymph node	RobTME	TaTME	LapTME

FIGURE 3 | Rank probability diagram. **(A)** CRM involvement; **(B)** CRM involvement for ISR; **(C)** Complete mesorectum; **(D)** Near complete mesorectum; **(E)** Incomplete mesorectum; **(F)** DRM involvement; **(G)** Tumor distance to the CRM; **(H)** DRM distance; **(I)** Harvested lymph nodes; **(J)** Summary of surgical approach rank in terms of surgical resection quality.

lower in operations for upper rectal cancer than for low rectal cancer operations in previous studies (68, 69). Furthermore, partial mesorectal excision (PME) with mesorectal transection 5 cm below the tumor is adequate for upper rectal cancers, while TME is necessary for mid-/low rectal cancer. This might decrease the diversity and strength of a network meta-analysis when performing indirect comparisons and calculating treatment rankings with probabilities among LapTME, RobTME, and TaTME. Last but not least, since the cutoff value for defining CRM positivity is still under debate, the threshold of 1 mm or less is the most commonly accepted and used in included studies (70). Rausa (8), in their network meta-analysis, also included the study by Velthuis, in which a positive CRM was defined as tumor involvement of 2 mm or less from the resection margin. The pooled result was therefore questionable due to a combination of CRM involvement rates with inconsistent definitions. In the present study, we included only mid-/low rectal cancers and defined CRM positivity with a threshold of 1 mm or less. Moreover, the sample sizes were relatively comparable among the different surgical approach groups.

Compared with the CRM, the mesorectal quality, or the so-called plane of mesorectal excision, represented a stricter and more precise indicator for assessing the degree of radical surgical resection. Since CRM involvement might occur when cT4 tumors grow directly into the circumferential margin, this cannot be considered incomplete removal of the surrounding mesorectum. Incomplete mesorectal excision might not always be related to CRM involvement in the case of a small tumor. In our study, there were no differences between these 3 surgical approaches regarding the quality of the specimen. RobTME ranked the best with a high probability of complete mesorectal excision. Furthermore, pooled network analysis observed a higher but not statistically significant risk of incomplete mesorectum when comparing both LapTME with RobTME (OR = 1.99) and LapTME with TaTME (OR = 1.90). However, we believe the results of the present study should be carefully interpreted. The incomplete mesorectal excision rate was obviously higher in the LapTME group (9.6%) than the rate of 1.9% in the RobTME group and of 5.6% in the TaTME group, even though these differences did not reach statistical significance. Additionally, a study based on postoperative magnetic resonance imaging (MRI) of the pelvis found that residual mesorectal tissue was detected in 3.1% of TaTME patients and 46.9% of LapTME patients, which indicated that the completeness of mesorectal excision was significantly better with TaTME than with the standard laparoscopic technique (71). Since the association of TME quality with prognosis was established in a previous large-scale RCT (72), the oncological outcomes of direct comparison among these 3 techniques when a negative CRM is combined with intact mesorectal excision should be awaited to specifically assess the surgical quality.

In laparoscopic surgery, it is challenging to accurately identify the distal margin and apply endoscopic staplers at a right angle to the rectum within the limited dissecting space. In TaTME, the tumor is distally approached through the anus, and the use of linear staplers can be avoided. This facilitates surgeons to accurately determine the DRM and logically secure a safe, adequate DRM length before rectal transection. Interestingly, however, we found a similar DRM positivity rate between LapTME (2.0%) and TaTME (1.9%), both of which were higher than the rate of RobTME (0.3%), even though the differences did not reach statistical significance. This could be explained by DRM involvement due to residual tumor cells beyond the regressed tumor edge after neoadjuvant chemoradiation. Surgeons might perform frozen sections to ensure oncologic clearance during TaTME for advanced tumors that have been subjected to neoadjuvant therapy. However, there is insufficient evidence in the literature regarding this issue. Moreover, it should be emphasized that the heterogeneity of the height of tumors from the anal verge and the proportion of neoadjuvant therapy might cause bias. In addition, RobTME was ranked the best with a high probability for the lowest rate of DRM involvement and longest DRM length in this study. These results are comparable to those of a recently published multicenter matched study (43) and a previous retrospective study (33). The potential advantage of RobTME regarding DRMs may be the result of technical advantages of the robotic approach because it allows the surgeon to perform high-quality maneuvers in the narrow pelvic cavity.

It is worth noting that TaTME was most likely to be ranked the worst in terms of CRM involvement for ISR in low rectal cancer. Larsen et al. (73) reported a 9.5% local recurrence rate at a median follow-up of 11 months among Norwegian rectal cancer patients who underwent TaTME. This rate is twice that of the rate observed in the COLOR II study (74), which included laparoscopic and open surgery cases, and has prompted the nationwide cessation of TaTME. In addition, these cases of local recurrence occurred early and with multifocal pelvic sidewall involvement. One explanation is that the rate of CRM involvement in TaTME for rectal cancers from this Norwegian national cohort was 12.7% (75), which was higher than the rates in RobTME and LapTME (67), consistent with our findings. The other explanation is due to the disadvantages of transanal dissection related to rectal transection and air flow during dissection from the perineum.

There were some limitations in our present study. First, except for 2 RCTs, the other studies included were all retrospective comparative studies, which created bias in the selection of patients for each minimally invasive procedure, especially during the learning curve period. However, coarsened exact matching was conducted by Lee, and propensity score matching analysis was performed by Persiani and Detering to eliminate selection bias. Moreover, our primary outcome of interest, the CRM, was routinely collected and objectively measured, thereby minimizing the problems of reporting bias due to the retrospective nature of the analysis. Second, the tumor response to neoadjuvant radiotherapy was demonstrated to have affected margin involvement (76). Although the CRM involvement rate was similar among these 3 approaches, the incomplete mesorectal excision rate was obviously higher in the LapTME group (9.6%) than the rate of 1.9% in the RobTME group and of 5.6% in the TaTME group, without a significant difference. Further RCTs stratified on the basis of neoadjuvant treatment are needed to specifically assess the surgical qualities of these 3 approaches. Third, although margin status and mesorectal excision completeness are important variables to assess resection quality, oncological outcomes are a multifactorial phenomenon. Long-term follow-up is awaited to assess the oncological outcomes among each minimally invasive procedure.

Based on the available data pooled from the most recent evidence, no difference was observed in terms of CRM involvement rates and all other qualities of surgical resection variables among RobTME, TaTME, and LapTME. Overall, RobTME was most likely to be ranked the best in terms of the quality of surgical resection for the treatment of mid-/low rectal cancer. In addition, TaTME should be performed with caution in the treatment of low rectal cancer.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

XW, ZZ, QY, SL, and PC conceived and designed the study. XW, QY, WG, XL, YH, and SH contributed to the computational analyses and confirmed the results. All authors contributed to the article and approved the submitted version.

FUNDING

This study was financially supported by the National Clinical Key Specialty Construction Project (General Surgery) of China (No. 2012-649), National Natural Science Foundation of China(81902378), Young Scientist Foundation of Fujian Provincial Commission of Health and Family Planning (2017-1-39) and the Startup Fund for Scientific Research, Fujian Medical University (No. 2017XQ1028), Joint Funds for the innovation of science and Technology, Fujian province (2017Y9038; 2017Y9103), Fujian Science and Technology Project (2016J01456), Natural Science Foundation of Fujian Province (2020J011030), Medical Science Research Foundation of Beijing Medical and Health Foundation (B20062DS), Fujian provincial health technology project (2020CXA025), Bethune Charitable Foundation (X-J-2018-004).

REFERENCES

1. Martling A, Singnomklao T, Holm T, Rutqvist LE, Cedermark B. Prognostic Significance of Both Surgical and Pathological Assessment of Curative Resection for Rectal Cancer. *Br J Surg* (2010) 91(8):1040–5. doi: 10.1002/bjs.4557
2. Wang CL, Qu G, Xu HW. The Short- and Long-Term Outcomes of Laparoscopic Versus Open Surgery for Colorectal Cancer: A Meta-Analysis. *Int J Colorectal Dis* (2014) 29(3):309–20. doi: 10.1007/s00384-013-1827-1
3. Stevenson ARL, Solomon MJ, Lumley JW, Peter H, Clouston AD, Gebski VJ, et al. Effect of Laparoscopic-Assisted Resection vs Open Resection on Pathological Outcomes in Rectal Cancer: The ALaCaRT Randomized Clinical Trial. *JAMA* (2015) 314(13):1356–63. doi: 10.1001/jama.2015.12009
4. James F, Megan B, Sargent DJ, Anne Marie B, Virgilio G, Maher A, et al. Effect of Laparoscopic-Assisted Resection vs Open Resection of Stage II or III Rectal Cancer on Pathologic Outcomes: The ACOSOG Z6051 Randomized Clinical Trial. *JAMA* (2015) 314(13):1346–55. doi: 10.1001/jama.2015.10529
5. Bianchi PP, Ceriani C, Locatelli A, Spinoglio G, Zampino MG, Sonzogni A, et al. Robotic Versus Laparoscopic Total Mesorectal Excision for Rectal Cancer: A Comparative Analysis of Oncological Safety and Short-Term Outcomes. *Surg Endoscopy Other Interventional Techniques* (2010) 24 (11):2888–94. doi: 10.1007/s00464-010-1134-7
6. Chang TC, Kiu KT. Transanal Total Mesorectal Excision in Lower Rectal Cancer: Comparison of Short-Term Outcomes With Conventional Laparoscopic Total Mesorectal Excision. *J Laparoendoscopic Adv Surg Tech A* (2018) 28:365–9. doi: 10.1089/lap.2017.0520
7. Simillis C, Lal N, Thoukididou SN, Kontovounisios C, Smith JJ, Hompes R, et al. Open Versus Laparoscopic Versus Robotic Versus Transanal Mesorectal Excision for Rectal Cancer: A Systematic Review and Network Meta-Analysis. *Ann Surg* (2019) 270:59–68. doi: 10.1097/SLA.0000000000003227
8. Rausa E, Bianco F, Kelly ME, Aiolfi A, Petrelli F, Bonitta G, et al. Systemic Review and Network Meta-Analysis Comparing Minimal Surgical Techniques for Rectal Cancer: Quality of Total Mesorectum Excision, Pathological, Surgical, and Oncological Outcomes. *J Surg Oncol* (2019) 119:987–98. doi: 10.1002/jso.25410
9. Nagtegaal ID, van de Velde CJ, van der Worp E, Kapiteijn E, Quirke P, van Krieken JH. Cooperative Clinical Investigators of the Dutch Colorectal Cancer Group. Macroscopic Evaluation of Rectal Cancer Resection Specimen: Clinical Significance of the Pathologist in Quality Control. *J Clin Oncol* (2002) 20(7):1729–34. doi: 10.1200/JCO.2002.07.010
10. Heald RJ, Ryall RD. Recurrence and Survival After Total Mesorectal Excision for Rectal Cancer. *Lancet* (1986) 327(8496):1479–82. doi: 10.1016/S0140-6736 (86)91510-2
11. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med* (2009) 6:e1000097. doi: 10.1371/journal.pmed.1000097
12. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the Quality of Reports of Randomized Clinical Trials: Is Blinding Necessary? *Control Clin Trials* (1996) 17:1–12. doi: 10.1016/0197-2456(95)00134-4
13. Wells GA, Shea BJ, O'Connell D, Peterson J, Welch V, Losos M, et al. *The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Non-Randomised Studies in Meta-Analyses*. Ottawa: Department of Epidemiology and Community Medicine, University of Ottawa (2005). Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
14. Ri HM, Won PJ, Sohee P, Hyekyoung Y, Dae Yong K, Hee Jin C, et al. Prognostic Impact of Circumferential Resection Margin in Rectal Cancer Treated With Preoperative Chemoradiotherapy. *Ann Surg Oncol* (2014) 21 (4):1345–51. doi: 10.1245/s10434-014-3484-1
15. Hozo SP, Djulbegovic B, Hozo I. Estimating the Mean and Variance From the Median, Range, and the Size of a Sample. *BMC Med Res Method* (2005) 5 (1):13. doi: 10.1186/1471-2288-5-13
16. Brooks SP, Gelman A. General Methods for Monitoring Convergence of Iterative Simulations. *J Comput Graphical Stat* (1998) 7(4):434–55. doi: 10.1080/10618600.1998.10474787
17. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring Inconsistency in Meta-Analyses. *BMJ* (2003) 327:557–60. doi: 10.1136/bmj.327.7414.557
18. Dias S, Welton NJ, Caldwell DM, Ades AE. Checking Consistency in Mixed Treatment Comparison Meta-Analysis. *Stat Med* (2010) 29(7–8):932–44. doi: 10.1002/sim.3767
19. Se Jin B, Sami AA, Duck Hyoun J, Hyuk H, Byung Soh M, Seung Hyuk B, et al. Robotic Versus Laparoscopic Coloanal Anastomosis With or Without Intersphincteric Resection for Rectal Cancer. *Surg Endoscopy* (2013) 27 (11):4157–63. doi: 10.1007/s00464-013-3014-4
20. Park SY, Choi GS, Park JS, Kim HJ, Ryuk JP. Short-Term Clinical Outcome of Robot-Assisted Intersphincteric Resection for Low Rectal Cancer: A Retrospective Comparison With Conventional Laparoscopy. *Surg Endoscopy* (2013) 27(1):48. doi: 10.1007/s00464-012-2405-2
21. Kuo LJ, Lin YK, Chang CC, Tai CJ, Chiou JF, Chang YJ. Clinical Outcomes of Robot-Assisted Intersphincteric Resection for Low Rectal Cancer: Comparison With Conventional Laparoscopy and Multifactorial Analysis of the Learning Curve for Robotic Surgery. *Int J Colorectal Dis* (2014) 29(5):555–62. doi: 10.1007/s00384-014-1841-y
22. Quentin D, Jean-Philippe A, Anne R, Etienne B, Christophe L, Eric R. Perineal Transanal Approach: A New Standard for Laparoscopic Sphincter-Saving Resection in Low Rectal Cancer, a Randomized Trial. *Ann Surg* (2014) 260 (6):993–9. doi: 10.1097/SLA.0000000000000766
23. Velthuis S, Nieuwenhuis DH, Ruijter TEG, Cuesta MA, Bonjer HJ, Sietses C. Transanal Versus Traditional Laparoscopic Total Mesorectal Excision for Rectal Carcinoma. *Surg Endoscopy* (2014) 28(12):3494–9. doi: 10.1007/s00464-014-3636-1

24. Park JS, Kim NK, Kim SH, Lee KY, Lee KY, Shin JY, et al. Multicentre Study of Robotic Intersphincteric Resection for Low Rectal Cancer. *Br J Surg* (2015) 102(12):1567–73. doi: 10.1002/bjs.9914
25. Serin KR, Gultekin FA, Batman B, Ay S, Kapran Y, Saglam S, et al. Robotic Versus Laparoscopic Surgery for Mid or Low Rectal Cancer in Male Patients After Neoadjuvant Chemoradiation Therapy: Comparison of Short-Term Outcomes. *J Robotic Surg* (2015) 9(3):187. doi: 10.1007/s11701-015-0514-3
26. Yoo BE, Cho JS, Shin JW, Lee DW, Kwak JM, Jin K, et al. Robotic Versus Laparoscopic Intersphincteric Resection for Low Rectal Cancer: Comparison of the Operative, Oncological, and Functional Outcomes. *Ann Surg Oncol* (2015) 22(4):1219–25. doi: 10.1245/s10434-014-4177-5
27. Chen CC, Lai YL, Jiang JK, Chu CH, Huang IP, Chen WS, et al. Transanal Total Mesorectal Excision Versus Laparoscopic Surgery for Rectal Cancer Receiving Neoadjuvant Chemoradiation: A Matched Case–Control Study. *Ann Surg Oncol* (2015) 23(4):1–8. doi: 10.1245/s10434-015-4997-y
28. De'Angelis N, Portigliotti L, Azoulay D, Brunetti F. Transanal Total Mesorectal Excision for Rectal Cancer: A Single Center Experience and Systematic Review of the Literature. *Langenbecks Arch Surg* (2015) 400 (8):945–59. doi: 10.1007/s00423-015-1350-7
29. María FH, Salvadora D, Antoni C, Marta T, Dulce M, Gabriel DDG, et al. Transanal Total Mesorectal Excision in Rectal Cancer: Short-Term Outcomes in Comparison With Laparoscopic Surgery. *Ann Surg* (2015) 261(2):221. doi: 10.1097/SLA.0000000000000865
30. Kanso F, Maggiori L, Debove C, Chau A, Ferron M, Panis Y. Perineal or Abdominal Approach First During Intersphincteric Resection for Low Rectal Cancer: Which Is the Best Strategy? *Dis Colon Rectum* (2015) 58(7):637. doi: 10.1097/DCR.0000000000000396
31. Perdawood SK, Al Khefagie GA. Transanal vs Laparoscopic Total Mesorectal Excision for Rectal Cancer: Initial Experience From Denmark. *Colorectal Dis* (2016) 18(1):51–8. doi: 10.1111/codi.13225
32. Bedirli A, Salman B, Yuksel O. Robotic Versus Laparoscopic Resection for Mid and Low Rectal Cancers. *Jsls J Soc Laparoendoscopic Surgeons* (2016) 20 (1):e2015.00110. doi: 10.4293/JSLS.2015.00110
33. Feroci F, Vannucchi A, Bianchi PP, Cantafio S, Garzi A, Formisano G, et al. Total Mesorectal Excision for Mid and Low Rectal Cancer: Laparoscopic vs Robotic Surgery. *World J Gastroenterol* (2016) 22(13):3602–10. doi: 10.3748/wjg.v22.i13.3602
34. Law WL, Foo DC. Comparison of Short-Term and Oncologic Outcomes of Robotic and Laparoscopic Resection for Mid-and Distal Rectal Cancer. *Surg Endoscopy* (2017) 31(7):2798–807. doi: 10.1007/s00464-016-5289-8
35. Lim DR, Bae SU, Hur H, Min BS, Baik SH, Kang YL, et al. Long-Term Oncological Outcomes of Robotic Versus Laparoscopic Total Mesorectal Excision of Mid–Low Rectal Cancer Following Neoadjuvant Chemoradiation Therapy. *Surg Endoscopy Other Interventional Techniques* (2016) 31(4):1–10. doi: 10.1007/s00464-016-5165-6
36. Canonico G, D''Alessandro A, Chouillard E. Transanal Notes Total Mesorectal Excision (TME) in Patients With Rectal Cancer: Is Anatomy Better Preserved? *Techniques Coloproctol* (2016) 44(4):1–8. doi: 10.1016/j.ejso.2018.01.060
37. Lelong B, Meillat H, Zemmour C, Poizat F, Ewald J, Mege D, et al. Short-And Mid-Term Outcomes After Endoscopic Transanal or Laparoscopic Transabdominal Total Mesorectal Excision for Low Rectal Cancer: A Single Institutional Case-Control Study. *J Am Coll Surgeons* (2017) 224(5):917–25. doi: 10.1016/j.jamcollsurg.2016.12.019
38. Marks JH, Montenegro GA, Salem JF, Shields MV, Marks GJ. Transanal TATA/TME: A Case-Matched Study of taTME Versus Laparoscopic TME Surgery for Rectal Cancer. *Techniques Coloproctol* (2016) 20(7):467–73. doi: 10.1007/s10151-016-1482-y
39. Rasulov AO, Mamedli ZZ, Gordeyev SS, Kozlov NA, Dzhumabaev HE. Short-Term Outcomes After Transanal and Laparoscopic Total Mesorectal Excision for Rectal Cancer. *Techniques Coloproctol* (2016) 20(4):227. doi: 10.1007/s10151-015-1421-3
40. Kim MJ, Park SC, Park JW, Chang HJ, Kim DY, Nam BH, et al. Robot-Assisted Versus Laparoscopic Surgery for Rectal Cancer: A Phase II Open Label Prospective Randomized Controlled Trial. *Ann Surg* (2017) 267(2):243. doi: 10.1097/SLA.0000000000002321
41. Perez D, Melling N, Biebl M, Reeh M, Baukloh JK, Miro J, et al. Robotic Low Anterior Resection Versus Transanal Total Mesorectal Excision in Rectal Cancer: A Comparison of 115 Cases. *Eur J Surg Oncol* (2018) 44:237–42. doi: 10.1016/j.ejso.2017.11.011
42. Perdawood SK, Thinggaard BS, Bjoern MX. Effect of Transanal Total Mesorectal Excision for Rectal Cancer: Comparison of Short-Term Outcomes With Laparoscopic and Open Surgeries. *Surg Endoscopy* (2018) 32:2312–21. doi: 10.1007/s00464-017-5926-x
43. Lee L, Lacy BD, Ruiz MG, Liberman AS, Albert MR, Monson JRT, et al. A Multicenter Matched Comparison of Transanal and Robotic Total Mesorectal Excision for Mid and Low-Rectal Adenocarcinoma. *Ann Surg* (2019) 270:1110–6. doi: 10.1097/SLA.0000000000002862
44. Seow-En I, Seow-Choen F. An Initial Experience Comparing Robotic Total Mesorectal Excision (RTME) and Transanal Total Mesorectal Excision (taTME) for Low Rectal Tumours. *Ann Acad Med Singapore* (2018) 47 (5):188–90.
45. Chen Y-T, Kiu K-T, Yen M-H, Chang T-C. Comparison of the Short-Term Outcomes in Lower Rectal Cancer Using Three Different Surgical Techniques: Transanal Total Mesorectal Excision (TME), Laparoscopic TME, and Open TME. *Asian J Surg* (2019) 42(6):674–80. doi: 10.1016/j.asjsur.2018.09.008
46. Detering R, Roodbeen SX, van Oostendorp SE, Dekker J-WT, Sietses C, Bemelman WA, et al. Three-Year Nationwide Experience With Transanal Total Mesorectal Excision for Rectal Cancer in the Netherlands: A Propensity Score Matched Comparison With Conventional Laparoscopic Total Mesorectal Excision. *J Am Coll Surgeons* (2019) 228(3):235–44.e1. doi: 10.1016/j.jamcollsurg.2018.12.016
47. Mege D, Hain E, Lakkis Z, Maggiori L, Prost à la Denise J, Panis Y. Is Trans-Anal Total Mesorectal Excision Really Safe and Better Than Laparoscopic Total Mesorectal Excision With a Perineal Approach First in Patients With Low Rectal Cancer? A Learning Curve With Case-Matched Study in 68 Patients. *Colorectal Dis* (2018) 20(6):O143–51. doi: 10.1111/codi.14238
48. Persiani R, Biondi A, Pennestrì F, Fico V, D'Ugo D. Transanal Total Mesorectal Excision vs Laparoscopic Total Mesorectal Excision in the Treatment of Low and Middle Rectal Cancer: A Propensity Score Matching Analysis. *Dis Colon Rectum* (2018) 61(7):1. doi: 10.1097/DCR.0000000000001063
49. Roodbeen SX, Penna M, Mackenzie H, Kusters M, Slater A, Jones OM, et al. Transanal Total Mesorectal Excision (TaTME) Versus Laparoscopic TME for MRI-Defined Low Rectal Cancer: A Propensity Score-Matched Analysis of Oncological Outcomes. *Surg Endosc* (2019) 33:2459–67. doi: 10.1007/s00464-018-6530-4
50. Rubinkiewicz M, Nowakowski M, Wierdak M, Mizera M, Dembiński M, Pisarska M, et al. Transanal Total Mesorectal Excision for Low Rectal Cancer: A Case-Matched Study Comparing TaTMe Versus Standard Laparoscopic TMe. *Cancer Manage Res* (2018) 10:5239. doi: 10.2147/CMAR.S181214
51. Heald RJ, Husband EM, Ryall RD. The Mesorectum in Rectal Cancer Surgery —the Clue to Pelvic Recurrence? *Br J Surg* (1982) 69:613–6. doi: 10.1002/bjs.1800691019
52. Leroy J, Jamali F, Forbes L, Smith M, Rubino F, Mutter D, et al. Laparoscopic Total Mesorectal Excision (TME) for Rectal Cancer Surgery: Long-Term Outcomes. *Surg Endoscopy Other Interventional Techniques* (2004) 18(2):281–9. doi: 10.1007/s00464-002-8877-8
53. Acuna SA, Chesney TR, Amarasekera ST, Baxter NN. Defining Non-Inferiority Margins for Quality of Surgical Resection for Rectal Cancer: A Delphi Consensus Study. *Ann Surg Oncol* (2018) 25(11):3171–8. doi: 10.1245/s10434-018-6639-7
54. Acuna S, Ramjist J, Baxter N, Chesney T. Laparoscopic Versus Open Resection for Rectal Cancer: A Non-Inferiority Meta-Analysis of Quality of Surgical Resection Outcomes. *Ann Surg* (2019) 269:849–55. doi: 10.1097/SLA.0000000000003072
55. Liu Q, Luo D, Cai S, Li Q, Li X. Circumferential Resection Margin as a Prognostic Factor After Rectal Cancer Surgery: A Large Population-Based Retrospective Study. *Cancer Med* (2018) 7:3673–81. doi: 10.1002/cam4.1662
56. Shin DW, Shin JY, Oh SJ, Park JK, Yu H, Ahn MS, et al. The Prognostic Value of Circumferential Resection Margin Involvement in Patients With Extraperitoneal Rectal Cancer. *Am Surgeon* (2016) 82(4):348. doi: 10.1177/000313481608200421
57. Wexner SD. Total Mesorectal Excision and Low Rectal Anastomosis for the Treatment of Rectal Cancer and Prevention of Pelvic Recurrences. *Techniques Coloproctol* (2001) 5(3):216–20. doi: 10.1001/archsurg.136.2.216

58. van der Pas MH, Haglind E, Cuesta MA, Fürst A, Lacy AM, Hop WC, et al. Laparoscopic Versus Open Surgery for Rectal Cancer (COLOR II): Short-Term Outcomes of a Randomised, Phase 3 Trial. *Lancet Oncol* (2013) 14 (3):210–8. van der Pas. doi: 10.1016/S1470-2045(13)70016-0
59. Guillou PJ, Quirke P, Thorpe H, Walker J, Jayne DG, Smith AM, et al. Short-Term Endpoints of Conventional Versus Laparoscopic-Assisted Surgery in Patients With Colorectal Cancer (MRC CLASICC Trial): Multicentre, Randomised Controlled Trial. *Lancet* (2005) 365(9472):1718–26. doi: 10.1016/S0140-6736(05)66545-2
60. Vignali A, Elmore U, Milone M, Rosati R. Transanal Total Mesorectal Excision (TaTME): Current Status and Future Perspectives. *Updates Surg* (2019) 71:29–37. doi: 10.1007/s13304-019-00630-7
61. Lacy AM, Tasende MM, Delgado S, Fernandez-Hevia M, Jimenez M, Lacy BD, et al. Transanal Total Mesorectal Excision for Rectal Cancer: Outcomes After 140 Patients. *J Am Coll Surgeons* (2015) 221(2):415–23. doi: 10.1016/j.jamcollsurg.2015.03.046
62. Deijen CL, Velthuis S, Tsai A, Mavroveli S, Klerk LD, Sietses C, et al. COLOR III: A Multicentre Randomised Clinical Trial Comparing Transanal TME Versus Laparoscopic TME for Mid and Low Rectal Cancer. *Surg Endoscopy Other Interventional Techniques* (2016) 30(8):3210–5. doi: 10.1007/s00464-015-4615-x
63. Hu D, Jin P, Hu L, Liu W, Zhang W, Guo T, et al. The Application of Transanal Total Mesorectal Excision for Patients With Middle and Low Rectal Cancer: A Systematic Review and Meta-Analysis. *Medicine* (2018) 97(28): e11410. doi: 10.1097/MD.0000000000011410
64. Wu Z, Zhou W, Chen F, Wang W, Feng Y. Short-Term Outcomes of Transanal Versus Laparoscopic Total Mesorectal Excision: A Systematic Review and Meta-Analysis of Cohort Studies. *J Cancer* (2019) 10(2):341. doi: 10.7150/jca.27830
65. Rubinkiewicz M, Czerwińska A, Zarzycki P, Małczak P, Nowakowski M, Major P, et al. Comparison of Short-Term Clinical and Pathological Outcomes After Transanal Versus Laparoscopic Total Mesorectal Excision for Low Anterior Rectal Resection Due to Rectal Cancer: A Systematic Review With Meta-Analysis. *J Clin Med* (2018) 7(11):448. doi: 10.3390/jcm7110448
66. Sun Y, Xu H, Li Z, Han J, Song W, Wang J, et al. Robotic Versus Laparoscopic Low Anterior Resection for Rectal Cancer: A Meta-Analysis. *World J Surg Oncol* (2016) 14(1):61. doi: 10.1186/s12957-016-0816-6
67. Jones K, Qassem MG, Sains P, Baig MK, Sajid MS. Robotic Total Meso-Rectal Excision for Rectal Cancer: A Systematic Review Following the Publication of the ROLARR Trial. *World J Gastrointest Oncol* (2018) 10(11):449–64. doi: 10.4251/wjgo.v10.i11.449
68. Hiranyakas A, Da Silva G, Wexner SD, Ho Y-H, Allende D, Berho M. Factors Influencing Circumferential Resection Margin in Rectal Cancer. *Colorectal Dis* (2013) 15(3):298–303. doi: 10.1111/j.1463-1318.2012.03179.x
69. Warrier SK, Kong JC, Guerra GR, Chittleborough TJ, Naik A, Ramsay RG, et al. Risk Factors Associated With Circumferential Resection Margin Positivity in Rectal Cancer: A Binational Registry Study. *Dis Colon Rectum* (2018) 61(4):433–40. doi: 10.1097/DCR.0000000000001026
70. Nagtegaal ID, Marijnen CAM, Kranenbarg EK, Van De Velde CJH, Van Krieken JHJM. Circumferential Margin Involvement Is Still an Important Predictor of Local Recurrence in Rectal Carcinoma: Not One Millimeter But Two Millimeters is the Limit. *Am J Surg Pathol* (2002) 26(3):350–7. doi: 10.1097/00000478-200203000-00009
71. Helbach MV, Koedam T, Knol J, Diederik A, Spaargaren G, Bonjer H, et al. Residual Mesorectum on Postoperative Magnetic Resonance Imaging Following Transanal Total Mesorectal Excision (TaTME) and Laparoscopic Total Mesorectal Excision (LapTME) in Rectal Cancer. *Surg Endoscopy* (2019) 33(1):94–102. doi: 10.1007/s00464-018-6279-9
72. Kitz J, Fokas E, Beissbarth T, Ströbel P, Wittekind C, Hartmann A, et al. Association of Plane of Total Mesorectal Excision With Prognosis of Rectal Cancer: Secondary Analysis of the CAO/ARO/AIO-04 Phase 3 Randomized Clinical Trial. *JAMA Surg* (2018) 153(8):e181607–e181607. doi: 10.1001/jamasurg.2018.1607
73. Larsen SG, Pfeffer F, Kørner H. Norwegian Colorectal Cancer Group. Norwegian Moratorium on Transanal Total Mesorectal Excision. *Br J Surg* (2019) 106(9):1120–1. doi: 10.1002/bjs.11287
74. Bonjer HJ, Deijen CL, Abis GA, Cuesta MA, van der Pas MHGM, de Lange-de Klerk ESM, et al. A Randomized Trial of Laparoscopic Versus Open Surgery for Rectal Cancer. *N Engl J Med* (2015) 372(14):1324–32. doi: 10.1056/NEJMoa1414882
75. Wasmuth HH, Faerden AE, Myklebust TÅ, Pfeffer F, Norderval S, Riis R, et al. Transanal Total Mesorectal Excision for Rectal Cancer has Been Suspended in Norway. *Br J Surg* (2020) 107(1):121–30. doi: 10.1002/bjs.11459
76. Rullier A, Gourgou-Bourgade S, Jarlier M, Bibeau F, Chassagne-Clément C, Hennequin C, et al. Predictive Factors of Positive Circumferential Resection Margin After Radiochemotherapy for Rectal Cancer: The French Randomised Trial ACCORD12/0405 PRODIGE 2. *Eur J Cancer* (2013) 49(1):82–9. doi: 10.1016/j.ejca.2012.06.028

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Oncology

ORIGINAL RESEARCH
published: 30 September 2021
doi: 10.3389/fonc.2021.762716

LongTerm Outcomes of Three-Port Laparoscopic Right Hemicolectomy *Versus* Five-Port Laparoscopic Right Hemicolectomy: A Retrospective Study

Tao Zhang[1†], Yaqi Zhang[1†], Xiaonan Shen[2†], Yi Shi[3], Xiaopin Ji[1], Shaodong Wang[1], Zijia Song[1], Xiaoqian Jing[1], Feng Ye[1*] and Ren Zhao[1*]*

[1] Department of General Surgery, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China, [2] Department of GI, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China, [3] Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, China

OPEN ACCESS

Edited by:
Tomoharu Sugie,
Kansai Medical University Hospital, Japan

Reviewed by:
Jiaying Miao,
Second Military Medical University, China
Ting Shi,
Second Military Medical University, China

****Correspondence:***
Ren Zhao
zhaorensurgeon@aliyun.com
Feng Ye
yefengsurgeon@163.com
Xiaoqian Jing
742842063@qq.com

†These authors have contributed equally to this work and share first authorship

Specialty section:
This article was submitted to Surgical Oncology, a section of the journal Frontiers in Oncology

Received: *22 August 2021*
Accepted: *01 September 2021*
Published: *30 September 2021*

Citation:
Zhang T, Zhang Y, Shen X, Shi Y, Ji X, Wang S, Song Z, Jing X, Ye F and Zhao R (2021) LongTerm Outcomes of Three-Port Laparoscopic Right Hemicolectomy Versus Five-Port Laparoscopic Right Hemicolectomy: A Retrospective Study. Front. Oncol. 11:762716. doi: 10.3389/fonc.2021.762716

Purpose: The aim of this study is to compare the long-term outcomes of three-port laparoscopic right hemicolectomy (TPLRC) and five-port laparoscopic right hemicolectomy (FPLRC) with retrospective analysis.

Methods: A total of 182 patients who accepted laparoscopic right hemicolectomy with either three ports (86 patients) or five ports (96 patients) from January 2012 to June 2017 were non-randomly selected and analyzed retrospectively.

Results: More lymph nodes were harvested in the TPLRC group than in the FPLRC group [17.5 (7), 14 (8) ml, $p < 0.001$]. There was less blood loss in the TPLRC group [50 (80) *vs.* 100 (125) ml, $p = 0.015$]. There were no significant differences in the other short-term or oncological outcomes between the two groups. The overall survival and disease-free survival were equivalent.

Conclusions: TPLRC is recommendable as it guarantees short- and long-term equivalent outcomes compared with FPLRC.

Keywords: colon cancer, laparoscopy, longterm outcomes, three-port laparoscopic right hemicolectomy, five-port laparoscopic right hemicolectomy, three-port laparoscopic assisted colectomy

INTRODUCTION

It has been three decades since Jacobs reported the first laparoscopic right hemicolectomy of the world in 1991 (1). The application of laparoscopic technology in colonic surgery has gradually become acceptable, even recommended. Multiple large-scale clinical studies (2–8) had proven its safety, feasibility, and equilibrium to laparotomy in oncological outcome and survival. These studies had made scientific judgment of laparoscopic technology and provided novel variations of laparoscopic surgery, such as single-incision laparoscopic surgery (SILS), port-reduced laparoscopic surgery, and so on. It was not until the year 2011 when, at almost the same time, a study on three-port laparoscopic colectomy of 24 patients was reported by Dr. Park from Korea (9) and a 49-case study was published by Dr. I. Seow-En from Singapore (10). After that, some small-scale clinical short-term outcomes of three-port laparoscopic colectomy, scattered in Egypt, Italy (11), and elsewhere, had been reported. Our center had published our short-term outcomes of three-port laparoscopic right hemicolectomy (TPLRC) *versus* five-port laparoscopic right hemicolectomy (FPLRC) in 2020, involving 168 patients and using a propensity score matching study, in which TPLRC presented non-inferiority to FPLRC (12). Years later, the long-term outcome of our study is to be described in this article.

MATERIALS AND METHODS

Patients and Collection

A retrospective chart review was performed on 182 patients with right hemi-colonic adenocarcinoma who received either TPLRC or FPLRC from January 2012 to June 2017 at Ruijin Hospital, Shanghai Jiao Tong University School of Medicine in China. Patients who were older than 80 upon receiving surgery, with stage IV colonic cancer concomitant with other malignant tumors, and with incomplete records for review were excluded. An approval of the study was granted by the Institutional Review Board of our hospital, and informed consent forms for the operations, from all patients, were recorded.

All the operations were performed by the same well-experienced surgeon who had completed more than 1,500 laparoscopic colorectal surgeries. A total of 86 patients who underwent TPLRC and 96 patients who went through a FPLRC were enrolled in this study.

The clinicopathologic information and perioperative outcomes were reviewed, including age, sex, body mass index, the American Society of Anesthesiologists grade, previous abdominal surgery, tumor site, operation time, estimated blood loss, time to cereal diet, length of postoperative hospital stay, postoperative complications, tumor size, number of harvested lymph nodes, proximal and distal resection margins, specimen length, lymph node metastasis, and pathologic stage according to the 8th edition of the AJCC Cancer Staging Manual. The postoperative complications were graded according to the Clavien–Dindo classification.

Follow-up surveillance was conducted in accordance with the National Comprehensive Cancer Network (NCCN) guidelines. Recurrence was confirmed by radiological or histological methods. Patients in stage III or stage II with high risk were routinely sent to chemotherapy for further treatment according to the guideline. For patients who presented with metastasis, a second-line chemotherapy was carried out, and standard evaluation was made to confirm whether surgery would be necessary.

Surgical Procedure

Position

The patients were placed in a lithotomy, Trendelenburg position. After the pneumo-peritoneum was established, the operation table was tilted to the left as appropriate to provide better exposure. In TPLRC, the surgeon was to the left of the patient, while the cameraman positioned between the legs of the patient. In FPLRC, the assistant was on the right side of the patient.

Trocar Placement

A trans-umbilical 12-mm port was inserted for the camera, and two others (5 and 12 mm) were placed at the left mid-clavicular line in TPLRC. There were two more ports in FPLRC, placed at the right mid-clavicular line or in another appropriate position (see **Figure 1**).

A vessel-priority D3 dissection + CME was carried out intracorporeally. The specimen was retrieved through an arc umbilical incision, with the wound protected (see **Figure 2**). Resection and anastomosis were performed extracorporeally by hand sutures or with a stapler (see **Figure 3**).

Statistical Analysis

Statistical analysis was performed with SPSS (version 23.0, SPSS Inc., Chicago, IL, USA). The statistically significant differences were evaluated using Mann–Whitney *U*-test, Student's *t*-test, χ^2 test, and Fisher exact test as appropriate. The overall survival and disease-free survival rates were estimated using the Kaplan–Meier method and compared using the log-rank test. A *p*-value <0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

There was no significant difference between the two groups in the baseline variables (see **Table 1**).

Intraoperative and Perioperative Outcomes

In the TPLRC group, less blood loss [50 (80) *vs*. 100 (125) ml, $p = 0.015$] was observed. There was no significant statistical difference between TPLRC and FPLRC with respect to operative time, length of postoperative hospital stay, time to cereal diet, and postoperative complications. Besides these, no case was converted to laparotomy, and there was neither readmission nor mortality within 30 days of surgery. There were three cases of grade III and IV complications in the three-port group: one case of anastomotic leakage which needed an intraperitoneal wash and two cases of cardiac dysfunction due to a very severe preoperative heart disease and who thus went to the intensive care unit after surgery. These patients were discharged afterwards with normal diet and New York Heart Association I–II (see **Table 2**). However, the distribution of complications showed no statistical difference in each group.

Pathologic and Oncologic Outcomes

More lymph nodes were harvested in the TPLRC group than in the FPLRC group [17.5 (7), 14 (8) ml, $p < 0.001$]. There were more T1 and T2 patients in the FPLRC group. The tumor size, proximal and distal resection margins, histology, metastatic

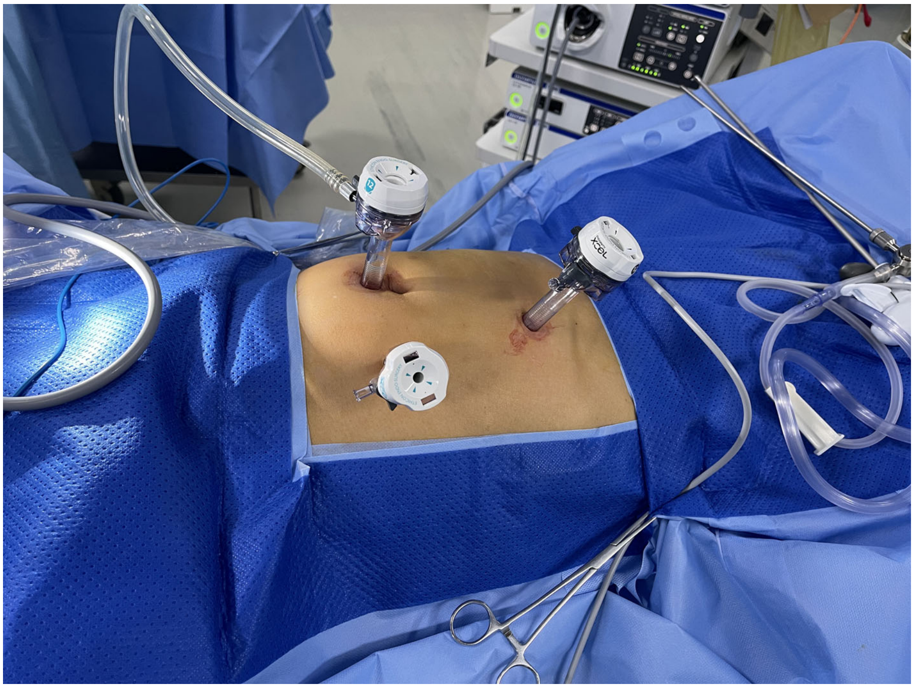


FIGURE 1 | Trocar placement.

FIGURE 2 | Incisions.

lymph node, and TNM stage manifested no difference between the TPLRC and FPLRC groups (see **Table 3**).

DFS and OS

In this study, the follow-up period ranges from 1 to 108 months. Eight patients (9.3%) in the TPLRC group and 13 patients (13.5%) in the FPLRC group were lost during the follow-up period (χ^2 = 0.799, P = 0.371). The median follow-up period was 72 months (95% CI, 68.89–75.11) in the TPLRC group and 82 months (95% CI, 72.92–91.08) in the FPLRC group (χ^2 = 2.837, p = 0.092).

The 5-year overall survival (OS) rates of the TPLRC and FPLRC groups were 79.6 and 70.9% (hazard ratio, HR: 0.642; 95% CI: 0.348–1.185; p = 0.150), respectively, and the 5-year disease-free survival (DFS) rates were 65.3 and 76.3% (HR, 0.646; 95% CI, 0.366–1.139; p = 0.124), respectively (see **Figures 4** and **5**).

Since the longest follow-up time reached 9 years, we also compared the 9-year OS and DFS rates of the two groups, and the results showed no statistical significance (p = 0.208 and p = 0.099).

DISCUSSION

Broadly speaking, the idea of laparoscopy can be traced back to ancient Rome. One of the inventors of the encyclopedia, a famous Roman doctor, Aulus Cornelius Celsus, first reported to have drained "evils humor" by using percutaneous devices (now called

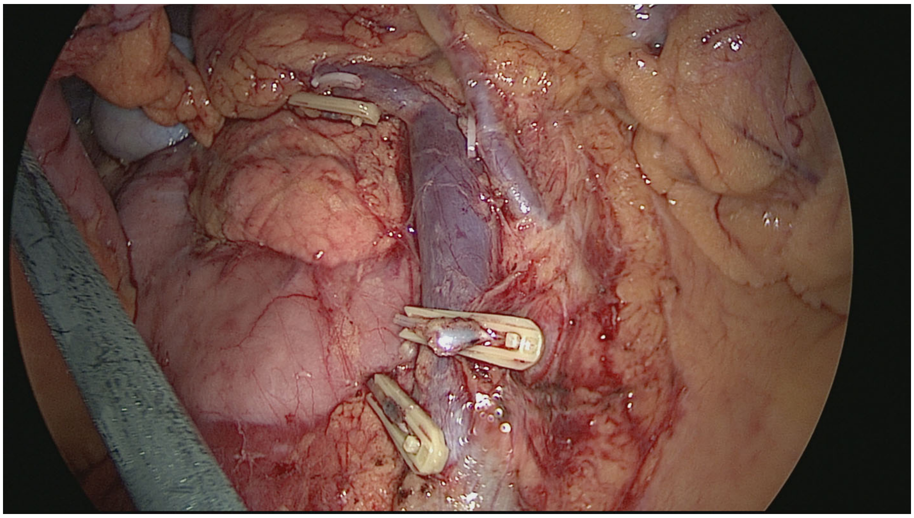


FIGURE 3 | A vessel-priority D3 dissection + CME.

TABLE 1 | Baseline characteristics.

Variable	Three-port (*N* = 86)	Five-port (*N* = 96)	Statistics	*P*-value
Age (year)				
Median (IQR)	62 (17)	66 (13)	Z = -1.174	0.240
Sex				
Male (%)	41 (47.7)	46 (47.9)	χ^2 = 0.001	0.974
Female (%)	45 (52.3)	50 (52.1)		
Body mass index				
<18.50 (%)	7 (8.1)	3 (3.1)	χ^2 = 0.003	0.954
18.50–24.99 (%)	61 (70.9)	60 (62.5)		
>24.99 (%)	18 (20.9)	33 (34.4)	χ^2 = 5.487	0.064
American Society of Anesthesiologists score				
I, II (%)	69 (80.2)	80 (83.3)	χ^2 < 0.001	
III, IV (%)	17 (19.8)	16 (16.7)	χ^2 = 0.294	0.701
Previous abdominal surgery (%)	25 (29.1)	33 (34.4)	χ^2 = 0.588	0.524
Tumor site				
Ileocecus (%)	21 (24.4)	34 (35.4)		
Ascending colon (%)	33 (38.4)	21 (21.9)		
Hepatic flexure (%)	24 (27.9)	33 (34.4)		
Transverse colon (%)	8 (9.3)	8 (8.3)	χ^2 = 6.631	0.085

TABLE 2 | Intraoperative and perioperative outcomes.

Variable	Three-port (*N* = 86)	Regular (*N* = 96)	Statistics	*P*-value
Operation time (min)				
Median (IQR)	140.0 (45.0)	150.0 (52.5)	Z = -1.861	0.063
Estimated blood loss, (ml)				
Median (IQR)	50.0 (80.0)	100.0 (125.0)	Z = -2.431	**0.015**
Postoperative hospital stays (days)				
Median (IQR)	9.0 (3.0)	9.0 (2.0)	Z = -0.845	0.398
Time to anal exhaust				
Median (IQR)	4.0 (2.0)	4.0 (2.0)	Z = 0.297	0.766
Time to liquid diet (days)				
Median (IQR)	6.0 (2.0)	5.0 (2.0)	Z = -0.310	0.976
Grade of complications				
0–I (%)	73 (84.9)	90 (92.8)		
II (%)	10 (11.6)	6 (6.3)		
III (%)	1 (1.2)	0 (0)		
IV (%)	2 (2.3)	0 (0)	χ^2 = 5.239	0.155

In bold: A p-value <0.05 was considered statistically significant.

trocars) (8, 13). Since then, particularly in the 20th century, the invention of a lighting system, telescopes, and insufflators and the integrity of all laparoscopic devices made the ancient dreams come true (14, 15). The first laparoscopic cholecystectomy (LC) of the world was performed by Mühe in the mid-1980s (13, 16, 17). After that, all varieties of laparoscopic-assisted surgery embraced its boom, and it would not take another 2000 years to make a leap and bounce in laparoscopic surgery.

Nowadays, laparoscopic surgery had confirmed its equality in safety and feasibility, better cosmetic outcome, and quicker recovery when compared with open surgery. A conventional laparoscopic colorectal surgery usually requires five or more trocars to insert instruments. With the increase in the number of trocars, the concomitant problems would increase accordingly. Postoperative incisional pain, incision-related wound infection, bleeding, hernia, or metastasis are not rare (18–20). Besides these, during the operation, unskilled assistants would sometimes interfere with the surgeon and even cause iatrogenic injury due to the so-called off-screen effect or violent tractions (21). The earliest reported clinical study about three-port laparoscopic colectomy dated back to 2011 (9, 10), and it is believed that many other surgeons had completed this kind of operations even earlier. We began to carry out three-port laparoscopic colectomy in 2012 in order to conquer the problem of shortage in surgical assistants. This point of view was identified with Jung Ryul Oh et al. (22) to carry out this operation with one surgeon and one cameraman. In this study, three-port surgery brags an advantage in less blood loss and

TABLE 3 | Pathologic and oncologic outcomes.

Variable	Three-port (*N* = 86)	Five-port (*N* = 96)	Statistics	*P*-value
Tumor size (cm)				
Median (IQR)	4.0 (2.0)	4.5 (2.0)	*Z* = -0.658	0.510
Specimen length (cm)				
Median (IQR)	27.0 (9.0)	28.0 (9.0)	*Z* = -0.403	0.687
Proximal resection margins, cm				
Median (IQR)	12.0 (8.0)	10.0 (7.3)	*Z* = -1.914	0.056
Distal resection margins, cm				
Median (IQR)	11.25 (8.0)	12.25 (10.5)	*Z* = -0.815	0.415
Lymph node harvest				
Median (IQR)	17.5 (7)	14 (8)	*Z* = -4.152	**<0.001**
Positive LN				
Median (IQR)	0 (1)	0 (1)	*Z* = -0.544	0.586
TNM stage				
I (%)	3 (3.4)	11 (11.3)	χ^2 = 6.085	0.193
II (%)	50 (7.5)	52 (53.6)		
III (%)	33 (37.9)	33 (34.0)		
T stage				
1, 2 (%)	3 (3.5)	15 (15.6)	*Z*	0.954
3, 4 (%)	83 (96.5)	81 (84.4)	χ^2 = 7.498	**0.006**
N stage				
0 (%)	52 (60.5)	63 (65.6)	χ^2 = 0.003	0.954
1 (%)	28 (32.6)	23 (24.0)	χ^2 = 0.003	0.954
2 (%)	6 (7.0)	10 (10.4)	χ^2 = 1.99	0.368

In bold: A p-value <0.05 was considered statistically significant.

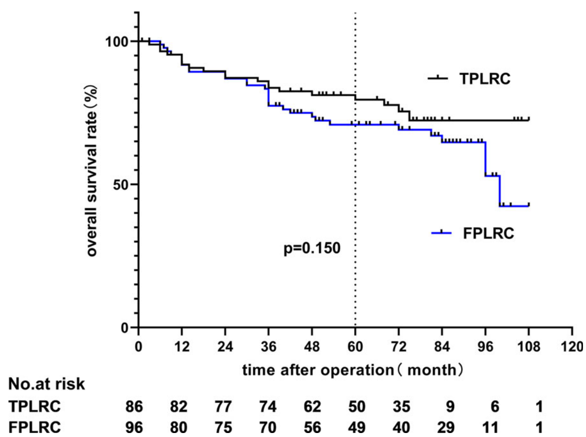


FIGURE 4 | Overall survival rate.

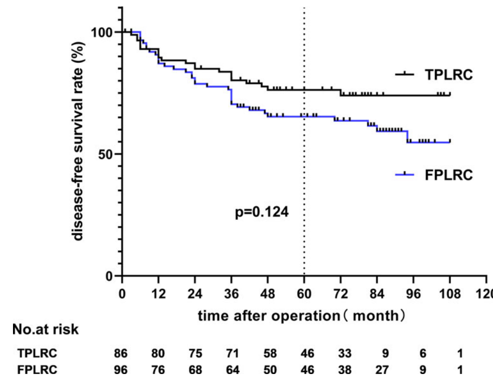


FIGURE 5 | Disease-free survival rate.

more lymph nodes harvested. The other perioperative and oncological outcomes presented no difference between the three-port and five-port groups. The distribution in postoperative complication presented no difference between the TPLRC and FPLRC groups. Although the intention of port-reduced laparoscopic surgery was to reduce port-related complications and others, there was one anastomotic leakage in the three-port group. The patient was concomitant with systemic lupus erythematosus with a long-time intake of glucocorticoid. It reminds us that careful selection of patients should be conducted preoperatively for the three-port surgery. Did the port-reduced surgery bring less pain to the patients compared to a conventional laparoscopic one? We have already denied the pain-ease theory in our previous article (12). Whether the cosmetic effect of port-reduced surgery can aesthetically please the patients is not reported in any of the present articles.

The clinical study about three-port laparoscopic-assisted colectomy (TLAC) is rarely reported. All we can search till now are retrospective analyses with short-term outcomes, in which TLAC possessed similar peri-operative and oncological outcomes as the five-port laparoscopic-assisted colectomy. In this study, we reviewed the laparoscopic right hemi-colectomy records and found out the long-term survival results. The average follow-up period exceeded 5 years, with the longest surveillance reaching 9 years in our study. OS and DFS manifested no difference between the TPLRC and FPLRC groups. Although there was no statistical difference between the 9-year OS, the separation of the curves is visible. Nine patients in the three-port group died from liver metastasis, two with lung metastasis and one with bone metastasis. Thirteen patients in the five-port group died from liver metastasis, two with lung metastasis and one with peritoneal metastasis. The main reason behind the difference may be the selection bias, and we cannot deny that there might have been an intention to choose some patients with earlier stage of the disease at the very beginning of the surgery, while the baseline of the two groups of patients presents no difference with statistical significance. Despite the controversy, this is hitherto the one and only long-term outcome ever reported, which can be an evidential support to recommend this kind of operation.

Geisler et al. (23) believe that the accumulation of TLAC is conducive to the development of single-incision surgery. Gash et al. (24) believe that the key to mastering single-incision laparoscopic colorectal surgery is developing TLAC surgery. Our center began the attempt of single-incision laparoscopic colectomy in December 2013. Passing the learning curve in SILS for sigmoid colon and upper rectum in our center took approximately 11 cases. Kirk et al. (25) reported 70 consecutive cases of SILS right hemi-colectomy, comparing the operation time, estimated bleeding, complications, and pathological results between the groups. Finally, about 40 cases were determined to pass through

LC. Haas et al. (26) reported about 30 to 36 cases of LC that can pass through the SILS of the right colon by the cumulative summation method. The essence of SILS is to move multiple ports to the same position; therefore, the development of three-port laparoscopic surgery is helping to shorten the LC of single-incision surgery. This point of view is consistent with the report of Haas et al. (26). However, due to the lack of a standardized comparison, the value of three-port surgical practice in shortening LC in single-incision surgery needs to be further evaluated.

This study has its limitation. The data was retrospectively collected, so selection bias could not be avoided, and the sample scale in this study is relatively not enough. In order to conquer the defect of a retrospective analysis, we have already conducted a single-center randomized control trial for this kind of operation.

CONCLUSIONS

In conclusion, TPLRC had an advantage in terms of less blood loss and more lymph nodes harvested and is non-inferior to FPLRC in all other variables, especially OS and DFS. Besides these, this kind of operation requires two trocars less than the conventional one, and only one surgeon and one cameraman were needed, which makes it worthy to recommend to experienced surgeons.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by a single center randomized controlled study of three-port laparoscopy and conventional laparoscopy assisted colorectal resection. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

RZ and TZ had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: TZ. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: TZ, YZ, and XS. Critical revision of the manuscript for important intellectual content: Statistical analysis: TZ and YZ. Obtained funding: RZ, XQJ, and TZ. Administrative, technical, or material support: All authors. Supervision: FY and RZ. All authors contributed to the article and approved the submitted version.

FUNDING

This study was supported by the National Natural Science Foundation of China [81902374 (XQJ)], the Shanghai Hospital Development Center [16CR2064B (RZ)], the Shanghai Municipal Health Construction Commission [201540026 (RZ)], and the Youth Development Program of Ruijin Hospital, Shanghai Jiaotong University School of Medicine [2019QNPY01010 (TZ)].

REFERENCES

1. Jacobs M, Verdeja JC, Goldstein HS. Minimally Invasive Colon Resection (Laparoscopic Colectomy). *Surg Laparosc Endosc* (1991) 1(3):144–50.
2. Jayne DG, Guillou PJ, Thorpe H, Quirke P, Copeland J, Smith AM, et al. Randomized Trial of Laparoscopic-Assisted Resection of Colorectal Carcinoma: 3-Year Results of the UK MRC CLASICC Trial Group. *J Clin Oncol* (2007) 25:3061–8. doi: 10.1200/JCO.2006.09.7758
3. Clinical Outcomes of Surgical Therapy Study Group. A Comparison of Laparoscopically Assisted and Open Colectomy for Colon Cancer. *N Engl J Med* (2004) 350:2050–9. doi: 10.1056/NEJMoa032651
4. Colon Cancer Laparoscopic or Open Resection Study Group. Survival After Laparoscopic Surgery *Versus* Open Surgery for Colon Cancer: Long- Term Outcome of a Randomised Clinical Trial. *Lancet Oncol* (2009) 10:44– 52. doi: 10.1016/S1470-2045(08)70310-3
5. Bonjer HJ, Deijen CL, Abis GA, Cuesta MA, van der Pas MHGM, de Lange-de Klerk ES, et al. A Randomized Trial of Laparoscopic *Versus* Open Surgery for Rectal Cancer. *N Engl J Med* (2015) 372:1324–32. doi: 10.1056/NEJMoa1414882
6. Jayne DG, Thorpe HC, Copeland J, Quirke P, Brown JM, Guillou PJ. Five-Year Follow-Up of the Medical Research Council CLASICC Trial of Laparoscopically Assisted *Versus* Open Surgery for Colorectal Cancer. *Br J Surg* (2010) 97:1638–45. doi: 10.1002/bjs.7160
7. Jeong SY, Park JY, Nam BH, Choi HS, Kim DW, Lim SB, et al. Open *Versus* Laparoscopic Surgery for Mid-Rectal or Low-Rectal Cancer After Neoadjuvant Chemoradiotherapy (COREAN Trial): Survival Outcomes of an Open-Label, Non-Inferiority, Randomised Controlled Trial. *Lancet Oncol* (2014) 15:767–74. doi: 10.1016/S1470-2045(14)70205-0
8. Hsieh C, Cologne KG. Laparoscopic Approach to Rectal Cancer-a New Standard? *Front Oncol* (2020) 10:1239. doi: 10.3389/fonc.2020.01239
9. Park JM, Suh SW, Kwak JM, Kim J, Kim S-H. Three-Port Laparoscopy-Assisted Colectomy for Colorectal Cancer Using External Traction With Suspension Suture. *Surg Laparosc Endosc Percutan Tech* (2011) 21(5):249–52. doi: 10.1097/SLE.0b013e31822ed88c
10. Seow-En I, Tan K-Y, Mohd Daud MAB. Traditional Laparoscopic Colorectal Resections Can Be Performed Effectively Using a Three-Port Technique. *Tech Coloproctol* (2011) 15(1):91–3. doi: 10.1007/s10151-010-0660-6
11. Currò G, Cogliandolo A, Lazzara S. Single-Incision *Versus* Three-Port Conventional Laparoscopic Right Hemicolectomy: Is There Any Real Need to Go Single? *J Laparoendosc Adv Surg Tech A* (2012) 22(7):621–4. doi: 10.1089/lap.2012.0120
12. Shi Y, Song Z, Gu Y, Zhang Y, Zhang T, Zhao R. Short-Term Outcomes of Three-Port Laparoscopic Right Hemicolectomy *Versus* Five-Port Laparoscopic Right Hemicolectomy: With a Propensity Score Matching Analysis. *J Invest Surg* (2020) 33(9):822–7. doi: 10.1080/08941939.2019.1579276
13. Spencer WG. *Trans. Celsus. De Medicina*. London: William Heinemann Ltd (1938). p. 1335.
14. Fourestier M, Gladu A, Vulmiere J. Presentation of a New Type of Bronchoscopic Material; Projection of Films. *J Fr Med Chir Thorac* (1952) 6:67–72.
15. Litynski GS. Kurt Semm and an Automatic Insufflator. *JSLS* (1998) 2:197–200.
16. Reynolds W Jr. The First Laparoscopic Cholecystectomy. *JSLS* (2001) 1:89–94.

17. Modlin IM, Kidd M, Lye KD. From the Lumen to the Laparoscope. *Arch Surg* (2004) 139:1110–26. doi: 10.1001/archsurg.139.10.1110
18. Swank HA, Mulder IM, la Chapelle CF, Reitsma JB, Lange JF, Bemelman WA. Systematic Review of Trocar-Site Hernia. *Br J Surg* (2012) 99(3):315–23. doi: 10.1002/bjs.7836
19. Zmora O, Gervaz P, Wexner SD. Trocar Site Recurrence in Laparoscopic Surgery for Colorectal Cancer. *Surg Endosc* (2001) 15(8):788–93. doi: 10.1007/s004640080151
20. Antoniou SA, Antoniou GA, Koch OO, Pointner R, Granderath FA. Blunt *Versus* Bladed Trocars in Laparoscopic Surgery: A Systematic Review and Meta-Analysis of Randomized Trials. *Surg Endosc* (2013) 27(7):2312–20. doi: 10.1007/s00464-013-2793-y
21. Leijte E, Arts E, Witteman B, Jakimowicz J, Blaauw ID, Botden S. Construct, Content and Face Validity of the Eosim Laparoscopic Simulator on Advanced Suturing Tasks. *Surg Endosc* (2019) 33(11):3635–43. doi: 10.1007/s00464-018-06652-3
22. Oh JR, Park SC, Park SS, Sohn B, Oh HM, Kim B, et al. Clinical Outcomes of Reduced-Port Laparoscopic Surgery for Patients With Sigmoid Colon Cancer: Surgery With 1 Surgeon and 1 Camera Operator. *Coloproctol* (2018) 34 (6):292–8. doi: 10.3393/ac.2018.04.06
23. Geisler D, Garrett T. Single Incision Laparoscopic Colorectal Surgery: A Single Surgeon Experience of 102 Consecutive Cases. *Tech Coloproctol* (2011) 15 (4):397–401. doi: 10.1007/s10151-011-0756-7
24. Gash KJ, Goede AC, Kaldowski B, Vestweber B, Dixon AR. Single Incision Laparoscopic (SILS) Restorative Proctocolectomy With Ileal Pouch-Anal Anastomosis. *Surg Endosc* (2011) 25(12):3877–80. doi: 10.1007/s00464-011-1814-y
25. Kirk KA, Boone BA, Evans L, Evans S, Bartlett DL, Holtzman MP. Analysis of Outcomes for Single-Incision Laparoscopic Surgery (SILS) Right Colectomy Reveals a Minimal Learning Curve. *Surg Endoscopy* (2015) 29(6):1356–62. doi: 10.1007/s00464-014-3803-4
26. Haas EM, Nieto J, Ragupathi M, Aminian A, Patel CB. Critical Appraisal of Learning Curve for Single Incision Laparoscopic Right Colectomy. *Surg Endoscopy* (2013) 27(12):4499–503. doi: 10.1007/s00464-013-3096-z

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Oncology

CLINICAL TRIAL
published: 25 October 2021
doi: 10.3389/fonc.2021.762147

Short-Term Outcomes of Single-Incision Laparoscopic Surgery for Colorectal Cancer: A Single-Center, Open-Label, Non-Inferiority, Randomized Clinical Trial

Zijia Song†, Kun Liu†, You Li†, Yiqing Shi, Yimei Jiang, Changgang Wang, Xianze Chen, Tao Zhang, Xiaopin Ji* and Ren Zhao**

Department of General Surgery, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China

Objective: To date, well-designed randomized controlled trials examining the safety, efficacy, and long-term outcomes of single-incision laparoscopic surgery (SILS) for colorectal cancer are scarce. The aim of the current study was to compare short-term outcomes of SILS for colorectal cancer with conventional laparoscopic surgery (CLS).

Methods: Between June 28, 2017, and June 29, 2019, a single-center, open-label, non-inferiority, randomized clinical trial was conducted at the Department of General Surgery, Ruijin Hospital (North), Shanghai Jiaotong University School of Medicine in Shanghai, China. In total, 200 patients diagnosed or suspected of colorectal cancer ($cT_{1–4a}N_{0–2}M_0$) were randomly assigned to either the SILS or CLS group in a 1:1 ratio. The primary outcome was early morbidity rate. Secondary outcomes included intraoperative outcomes, pain intensity, postoperative recovery, pathologic outcomes, and long-term outcomes.

Results: In total, 193 participants (SILS, 97; CLS, 96) were analyzed in the modified intention-to-treat (MITT) population. Among them, 48 underwent right hemicolectomy (SILS $n = 23$, 23.7% and MLS $n = 25$, 26%), 15 underwent left hemicolectomy (SILS $n = 6$, 6.2% and MLS $n = 9$, 9.4%), 1 underwent transverse colectomy (MLS $n = 1$, 1%), 57 underwent sigmoidectomy (SILS $n = 32$, 33% and MLS $n = 25$, 26%), and 72 underwent anterior resection (SILS $n = 36$, 37.1% and MLS $n = 36$, 37.5%). No significant differences were observed in the baseline characteristics. The intraoperative complication was comparable between the two groups [5 (5.2%) vs. 4 (4.2%); difference, 1%; 95% CI, –5.8% to 7.8%; $p > 0.999$) and so was postoperative complication rates [10 (10.3%) vs. 14 (14.6%); difference, –4.3%; 95% CI, –13.9% to 5.3%; $p = 0.392$]. The SILS group showed shorter incision length [median (IQR), 4 (3.5–5) vs. 6.6 (6–7.5), $p < 0.001$] and lower VAS scores on the first [median (IQR), 4 (3–5) vs. 4 (4–5), $p = 0.002$] and the second day [median (IQR), 2 (1.5–3) vs. 3 (2–4), $p < 0.001$] after surgery. No statistically significant difference was found in other measured outcomes.

Edited by:
Francesco Giovinazzo,
Catholic University of the Sacred Heart, Italy

Reviewed by:
Baochi Ou,
First Affiliated Hospital of Anhui Medical University, China
Hang Zhou,
Harbin Medical University, China

***Correspondence:**
Tao Zhang
woodyhom@yahoo.com
Xiaopin Ji
surgeonjee@hotmail.com
Ren Zhao
zhaorensurgeon@aliyun.com

†These authors have contributed equally to this work and share first authorship

Specialty section:
This article was submitted to Surgical Oncology, a section of the journal Frontiers in Oncology

Received: 21 August 2021
Accepted: 05 October 2021
Published: 25 October 2021

Citation:
Song Z, Liu K, Li Y, Shi Y, Jiang Y, Wang C, Chen X, Zhang T, Ji X and Zhao R (2021) Short-Term Outcomes of Single-Incision Laparoscopic Surgery for Colorectal Cancer: A Single-Center, Open-Label, Non-Inferiority, Randomized Clinical Trial. Front. Oncol. 11:762147. doi: 10.3389/fonc.2021.762147

Conclusions: Compared with CLS, SILS performed by experienced surgeons for selected colorectal cancer patients is non-inferior with good short-term safety and has the advantage of reducing postoperative pain.

Clinical Trial Registration: ClinicalTrials.gov, identifier NCT03151733.

Keywords: colorectal cancer, single-incision laparoscopic surgery, multiport laparoscopic surgery, short-term outcomes, randomized controlled trial

INTRODUCTION

At present, surgery is among the most important treatments for colorectal cancer. Laparoscopic surgery is becoming a major option since several randomized controlled trials (1–6) have demonstrated its safety, effectiveness, and benefits in less intraoperative blood loss, faster recovery, less postoperative pain, shorter hospital stays, etc. compared with laparotomy. With the continuous development of minimally invasive technology and instruments, more and more studies focus on further reducing surgical trauma. Single-incision laparoscopic surgery (SILS) is attracting increasingly more attention as an attempt to transition to "scarless" surgery. It has been a decade since Bucher et al. (7) first reported SILS for colon cancer, and this technique is considered to be the next major advance in the evolution of minimally invasive surgical approaches to colorectal disease feasible in generalized use (8). However, to date, the technique is still in its early stage and is controversial, especially regarding its technical challenges, safety in rectal cancer, potential benefits of reducing postoperative pain and better cosmetic effects, and long-term oncological outcomes (9–11). The evidence is too sparse to allow any firm recommendation. Therefore, more studies, especially large-scale, prospective, randomized controlled trials are needed to further evaluate its application in colorectal cancer. Our center first performed SILS for colorectal cancer in December 2013 and found it to be a safe and feasible option, which inspired us to conduct this RCT to test the hypothesis. Patients are still being followed up and the short-term outcomes of the study are presented here.

MATERIALS AND METHODS

Design

This single-center, open-label, prospective, randomized, non-inferiority trial (ClinicalTrials.gov identifier: NCT03151733) was conducted at the Department of General Surgery, Ruijin Hospital (North), Shanghai Jiaotong University School of Medicine in Shanghai, China. The study protocol and the informed consent documents were approved by the Clinical Trial Ethics Committee of Ruijin Hospital (North).

Participants

Patients aged 18 to 85, diagnosed with or suspected of colorectal cancer with clinical stage of $cT_{1-4a}N_{0-2}M_0$, were screened for inclusion. Considering the controversy of laparoscopic surgery for lower rectal cancer and the SILS technical difficulties, patients with body mass index (BMI) >30 kg/m (2), tumor size >5 cm, gastrointestinal surgery history (apart from appendicectomy), or tumor lower border located distal to the peritoneal reflection were excluded. The detailed inclusion, exclusion, and withdrawal criteria are shown in **Table 1**. Written informed consents were received from all participants.

Randomization and Masking

Eligible patients were randomly assigned to either the SILS or conventional laparoscopic surgery (CLS) group in a 1:1 ratio. The data inspector, who did not participate in patient screening and enrollment, performed the randomization using the random number table method. The allocation sequence was concealed from the surgeons until participants were formally assigned to their groups, using sequentially numbered, identical, opaque, sealed envelopes. Operative procedures and postoperative treatment were not concealed from the patients or investigators.

Surgical Procedures

Six qualified surgeons with over 50 cases of experience of laparoscopic colorectal cancer surgery performed the operations in the CLS group, while the SILS group operations were all performed by the same surgeon (RZ), who had performed over 100 cases of SILS for colorectal cancer before the trial began.

After general anesthesia, the patients were placed in optimal positions according to the surgical approach. In general, straddle-type supine, Trendelenberg with left-tilted or right-titled position was used in right colectomy or left colectomy, respectively, and modified lithotomy, Trendelenberg, right-tilted position was used in sigmoidectomy and anterior resection.

In the SILS group, a SILS™ Port (Covidien, Mansfield, MA, USA) with three 5-mm cannulas inserted or a Star-Port (Surgaid®, Guangzhou, China) consisting of three fixed instrument channels (one 5 mm, two 10 mm, and one 12 mm) was installed through a 2~3 cm in length midline periumbilical incision. A 30° laparoscope, a 0° flexible laparoscope (LTF-VP, Olympus Medical Systems, Tokyo, Japan), or an Olympus 3D laparoscope was used based on the choice of port. In cases using the SILS™ Port, the main operating cannula was changed from 5 to 12 mm when using Endo GIA™. In the CLS group, the operation was performed with 3 to 5 trocars including a 12-mm trocar for a 30° laparoscope or a 3D laparoscope in the periumbilical area. The main operating trocar was 12 mm, while the remaining trocars were 5 mm. All operations in both groups were performed using conventional laparoscopic instruments.

TABLE 1 | Inclusion, exclusion, and withdrawal criteria.

Inclusion criteria	Exclusion criteria	Withdrawal criteria
• 18 years < age < 85 years	• BMI > 30 kg/m (2)	• Intraoperative or pathological confirmation of invasion of adjacent structures or distant metastasis
• Pathological or highly suspected colorectal carcinoma	• The lower border of the tumor is located distal to the peritoneal reflection	• Non-colorectal adenocarcinoma confirmed by postoperative pathology
• Tumor located in the colon and rectum (the lower border of the tumor is above the peritoneal reflection)	• Previous gastrointestinal surgery (apart from appendicectomy)	• Requirement of emergency operation due to the change of illness state
• Clinically diagnosed $cT_{1-4a}N_{0-2}M_0$ lesions according to the seventh Edition of AJCC Cancer Staging Manual	• Emergency operation due to complication caused by colorectal cancer (bleeding, perforation, or obstruction)	• Inability to undergo surgery or anesthesia due to the change of illness state
• Tumor size of ≤5 cm	• Requirement of simultaneous surgery for other disease	• Unable to complete the clinical trial due to various reasons
• Performance status ECOG 0–1	• Pregnancy or lactation	• Patient required to withdraw
• ASA class I to III	• Severe mental disease	
• Informed consent	• Simultaneous or metachronous multiple cancers with disease-free survival ≤5 years	

BMI, body mass index; ASA, The American Society of Anesthesiologists; ECOG, Eastern Cooperative Oncology Group.

All the operations were performed according to the same oncologic principles, including complete mesocolic excision (CME) for colon cancer and total mesorectal excision (TME) for rectal cancer with D3 lymph node dissection. The medial-to-lateral or lateral-to-medial approach was at the discretion of the surgeon. For sigmoidectomy and anterior resection, mobilization of the splenic flexure was not performed routinely except in cases of a lack of redundancy of the sigmoid colon or excessive anastomotic tension. Depending on the anastomosis, the prophylactic ileostomy may be performed.

The specimen was retrieved through the wound protector installed through the transumbilical incision (SILS group) or a 3- to 4-cm additional incision (CLS group). The draining tube was extracted through the incision in the SILS group or through the main operating channel in the CLS group. The closure of incisions was done by absorbable monofilament. The details of the operative procedure were described in our previous reports (12, 13).

Perioperative Management

The perioperative management was similar between the two groups. All the patients underwent mechanical bowel preparation and oral antibiotic prophylaxis 1 day before surgery. The Foley catheters for patients who underwent anterior resections were removed after bladder training by clamping, while others were removed on postoperative day 1. Pain was controlled exclusively within 48 h after operation by patient-controlled analgesia (PCA, 100 ml) composed of 2 μ g/kg sufentanil citrate and 100 mg flurbiprofen axetil. The PCA continued to infuse at 2 ml/h. If the pain could not be tolerated, the patient could receive a bolus dose of 2 ml, with a locking time of 20 min between the doses. Additional analgesics were allowed in cases of breakthrough pain. Patients were allowed to drink water after first passage of flatus and then gradually transitioned to a liquid and soft diet. The drainage tube was removed 1~2 days after restoration of soft diet. Discharge was considered when the following conditions were met: no fever or other signs of complications and tolerating soft diet and controlled pain without any analgesics.

Outcomes

The primary outcome was early morbidity defined as the postoperative complications observed within 30 days after surgery. It was graded according to the Clavien–Dindo classification. The secondary outcomes included intraoperative outcomes (operation time, estimated blood loss, incision length, conversion rate), postoperative pain score, postoperative recovery (time to first ambulation, flatus, liquid diet and soft diet, length of hospital stay), pathologic outcomes (tumor size, number of harvested lymph nodes, proximal and distal resection margins), and long-term outcomes (5-year incision hernia rate, 3-year disease free survival rate, 5-year overall survival rate). The incision length was defined as the sum of all incision lengths. Postoperative pain was recorded using the visual analog scale (VAS) pain score (0–10 points) on postoperative days 1, 2, and 3. The pathologic outcomes were evaluated by pathologists. The follow-up was consistent with the National Comprehensive Cancer Network (NCCN) guidelines. Recurrence was confirmed by radiological or histological methods.

Sample Size Estimation

Sample size estimation was performed with PASS (11th edition, NCSS, LLC, UT, USA). According to previous data of our center, primary endpoint (early morbidity rate) was estimated to be 14% and 10%, respectively, in the CLS group and SILS group. The sample size was determined with one-side alpha of 0.025, a power of 0.8, and a non-inferiority margin of 10%. Assuming a dropout rate of 15%~20%, the sample size was estimated as 200 (100 per group).

Statistical Analysis

Statistical analysis was performed with SPSS (version 22.0, SPSS Inc., Chicago, IL, USA). Continuous data were described as means with standard deviations (SD) or median with interquartile ranges (IQR), and categorical data were described as frequencies and percentages. Statistically significant differences were evaluated using the Mann–Whitney *U* test, Student's *t*-test, χ^2 test, and Fisher's exact test, as appropriate. A two-sided *p*-value <0.05 was considered statistically significant.

Data were analyzed in the modified intention-to-treat (MITT) population.

RESULTS

Between June 28, 2017, and June 29, 2019, 200 patients were randomly assigned to either the SILS or CLS group. A total of 193 patients [SILS: 97, of whom 56 were male (57.7%), with a median (IQR) age of 63 (54.5–69) years; CLS: 96, of whom 54 were male (56.3%), with a median (IQR) age of 65 (56–70) years] were analyzed in the MITT population (**Figure 1**). Forty-nine right hemicolectomy (SILS: 23, 23.7% and CLS: 26, 27.1%), 15 left hemicolectomy (SILS: 6, 6.2% and CLS 9, 9.4%), 1 transverse colectomy (CLS: 1, 1%), 55 sigmoidectomy (SILS: 31, 32% and CLS: 24, 25%), and 73 anterior resection (SILS: 37, 38.1% and CLS: 36, 37.5%) were performed. The baseline characteristics were well balanced between the groups (**Table 2**).

Intraoperative and Postoperative Outcomes

The intraoperative and postoperative outcomes are shown in **Table 3**. The median (IQR) operation time was similar between the groups [120 (90–132) vs. 120 (96.3–148.3) min, $p = 0.262$]. No conversion occurred in the CLS group, while 14 patients (14.4%) used additional trocars (all cases plus one trocar) and 1 patient (1%) converted to laparotomy in the SILS group. The reasons for additional trocars were intraperitoneal adhesion ($n = 3$, 3.1%), vascular injury ($n = 4$, 4.1%), adjacent organ injury ($n = 1$, 1%), poor surgical exposure ($n = 4$, 4.1%), and dissection difficulties ($n = 2$, 2.1%). The reason for laparotomy was dissection difficulties. The median (IQR) incision length was significantly shorter in the SILS group [4 (3.5–5) vs. 6.6 (6–7.5) cm, $p < 0.001$]. The median (IQR) VAS scores in the SILS group were lower on postoperative day 1 (POD1) [4 (3–5) vs. 4 (4–5), $p = 0.002$] and POD2 [2 (1.5–3) vs. 3 (2–4), $p < 0.001$]. The usage of additional postoperative analgesics within 3 days after surgery was comparable between the two groups [13 (13.4%) vs. 11 (11.5%), $p = 0.828$]. The estimated blood loss and recovery from surgery did not differ statistically between the two groups.

The intraoperative complication [5 (5.2%) vs. 4 (4.2%); difference, 1%; 95% CI, −5.8% to 7.8%; $p > 0.999$] and postoperative complication rates [10 (10.3%) vs. 14 (14.6%), $p = 0.392$] were comparable between the two groups. Non-inferiority of SILS compared with CLS demonstrated as the upper limit of the 95% confidence interval (CI) for between-group difference calculated by the Newcombe method was less than the non-inferiority margin of 10% (postoperative complication rate difference, −4.3%; 95% CI, −13.9% to 5.3%). One patient (1%) in the SILS group had splenic injury during left hemicolectomy. The other eight patients (SILS: 4, 4.1%; CLS: 4, 4.2%) were vascular injury. The postoperative complications of

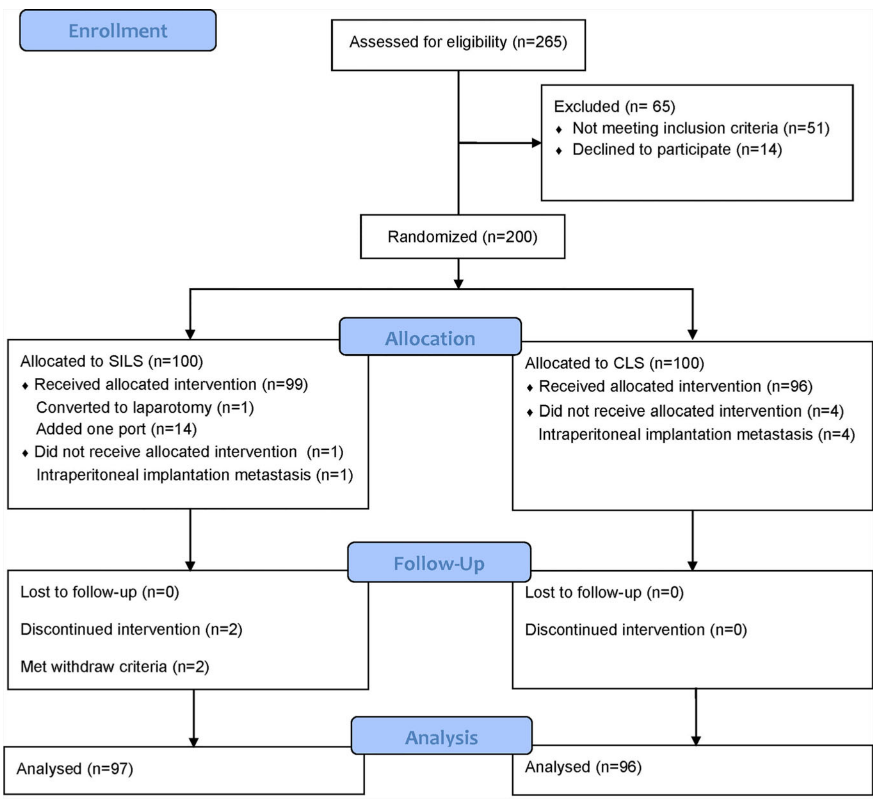


FIGURE 1 | Consort flow diagram.

TABLE 2 | Baseline characteristics.

Characteristics	SILS (*n* = 97)	CLS (*n* = 96)
Age (years)[a]	63 (54.5–69)	65 (56–70)
Sex ratio (M:F)	56:41	54:42
BMI (kg/m²)[b]	23.0 (2.8)	23.6 (3.2)
ASA grade		
I	40 (41.2)	29 (30.2)
II	47 (48.5)	53 (55.2)
III	10 (10.3)	14 (14.6)
Comorbidities	51 (52.6)	53 (55.2)
Previous abdominal surgery	23 (23.7)	26 (27.1)
ECOG score		
0	43 (44.3)	36 (37.5)
1	54 (55.7)	60 (62.5)
Procedure performed		
Right hemicolectomy	23 (23.7)	26 (27.1)
Left hemicolectomy	6 (6.2)	9 (9.4)
Transverse colectomy	0 (0)	1 (1)
Sigmoidectomy	31 (32.0)	24 (25.0)
Anterior resection	37 (38.1)	36 (37.5)

Values in parentheses are percentages unless indicated otherwise.
BMI, body mass index; ASA, The American Society of Anesthesiologists; ECOG, Eastern Cooperative Oncology Group.
[a]Values are mean (SD).
[b]Values are median (IQR).

TABLE 3 | Intraoperative and postoperative outcomes.

Variable	SILS (*n* = 97)	CLS (*n* = 96)	*P*[a]
Operation time (min)[b]	120 (90–132)	120 (96.3–148.3)	0.262[c]
Estimated blood loss (ml)[b]	50 (10–100)	50 (20–100)	0.067[c]
Conversions	15 (15.5)	0 (0)	
Laparotomy	1 (1)	0 (0)	>0.999
Additional trocar	14 (14.4)	–	
Incision length (cm)[b]	4 (3.5–5)	6.6 (6–7.5)	<0.001[c]
Time to first ambulation (h)[b]	48 (24–48)	48 (48–72)	0.054[c]
Time to flatus (h)[b]	48 (46.5–72)	48 (48–72)	0.341[c]
Time to liquid diet (days)[b]	5 (5–6)	5 (5–6)	0.501[c]
Time to soft diet (days)[b]	7 (6–7)	7 (6–7.8)	0.763[c]
Length of hospital stay (days)[b]	8 (8–10)	8 (8–10)	0.613[c]
Postoperative pain score (VAS)[b]			
POD1	4 (3–5)	4 (4–5)	0.002[c]
POD2	2 (1.5–3)	3 (2–4)	<0.001[c]
POD3	1 (1–2)	1.5 (1–2)	0.316[c]
Additional postoperative analgesics	13 (13.4)	11 (11.5)	0.828
POD1	10 (10.3)	5 (5.2)	0.282
POD2	6 (6.2)	8 (8.3)	0.592
POD3	3 (3.1)	3 (3.1)	>0.999
Intraoperative complications	5 (5.2)	4 (4.2)	>0.999
Vascular injury	4 (4.1)	4 (4.2)	
Adjacent organ injury	1 (1)	0 (0)	
Postoperative complications	10 (10.3)	14 (14.6)	0.392
Peritoneal effusion	2 (2.1)	2 (2.1)	
Anastomotic leakage	3 (3.1)	1 (1)	
Wound infection	4 (4.1)	2 (2.1)	
Anastomotic hemorrhage	0 (0)	1 (1)	
Intra-abdominal hemorrhage	0 (0)	1 (1)	
Ileus	0 (0)	2 (2.1)	
Urinary retention	0 (0)	2 (2.1)	
CVC infection	0 (0)	1 (1)	
FUO	1 (1)	2 (2.1)	
Grade of complications			0.669
I	7 (7.2)	9 (9.4)	
II	1 (1)	3 (3.1)	
IIIa	0 (0)	1 (1)	
IIIb	2 (2.1)	1 (1)	
Reoperation	2 (2.1)	1 (1)	>0.999
Readmission within 30 days of surgery	1 (1)	0 (0)	>0.999
Mortality within 30 days of surgery	0 (0)	0 (0)	–

Values in parentheses are percentages unless indicated otherwise.
VAS, visual analog score; POD, postoperative day; CVC, central venous catheters; FUO, fever of unknown origin.
[a]χ^2 or Fisher's exact test.
[b]Values are median (IQR).
[c]Mann–Whitney U test.

the SILS group included two (2.1%) peritoneal effusion (grade I), three (3.1%) anastomotic leakages (grade IIIa: 1, 1%; grade IIIb: 2, 2.1%), four (4.1%) wound infections (grade I), and one (1%) fever of unknown origin (FUO, grade I). The postoperative complications of the CLS group included two (2.1%) peritoneal effusion (grade I), one (1%) anastomotic leakage (grade IIIb: 1), two (2.1%) wound infections (grade I), one (1%) anastomotic hemorrhage (grade I), one (1%) intra-abdominal hemorrhage (grade II), two (2.1%) ileus (grade II), one (1%) urinary retention (grade IIIa), one (1%) central venous catheter infection (grade I), and one (1%) FUO (grade I). Two patients (SILS: 1, 1%; CLS: 1, 1%) performed emergency reoperation with diverting ileostomy during the hospitalization. One patient (1%) in the SILS group was readmitted for anastomotic leakage 2 days after discharge and performed diverting ileostomy. There was no mortality within 30 days after surgery in either group.

Pathologic Outcomes

Regarding the pathologic outcomes, the tumor size, proximal and distal resection margins, number of harvested lymph nodes, cell type, neurovascular invasion, and pathologic stage were similar between the two groups (**Table 4**). In the cases of rectal cancer, no positive circumferential resection margin was found.

DISCUSSION

To the best of our knowledge, seven RCT studies (9, 11, 14–19) have been published on SILS for colorectal cancer, including three multicenter studies (9, 11, 18, 19). However, these studies all had limitations. The conclusions of four previous RCT studies (14–17) may be less reliable because of the inadequate sample size calculations. Besides, in the multicenter study of Maggiori et al. (19), the application value of SILS for colorectal cancer could not be well evaluated since both benign and malignant cases were included and the sample size of malignant cases was small (18 patients each group). The SIMPLE trial (9) was the best designed RCT to date, with the largest sample size and multicenter participation. However, similar to an earlier multicenter RCT study in Japan (11, 18), it excluded patients with rectal, descending colon, and transverse colon cancers. Thus, we try to overcome such limitation and add more evidence to the literature while conducting the present study.

In the present study, the non-inferiority was met and the early morbidity was comparable between the SILS and CLS groups.

TABLE 4 | Pathologic outcomes.

Variable	SILS (*n* = 97)	CLS (*n* = 96)	*P*[a]
Tumor size (cm)[b]	3.5 (2.5–4)	4 (3–4.5)	0.071[c]
Proximal resection margins (cm)[b]	6 (4–9)	6 (4.1–9.9)	0.422[c]
Distal resection margins (cm)[b]	4 (2.8–7)	4.4 (2.5–7.9)	0.527[c]
Harvested lymph nodes[b]	13 (10–15)	13 (10.2–15)	0.952[c]
Cell type			0.195
WD/MD	50 (51.5)	40 (41.7)	
PD/others	47 (48.5)	56 (58.3)	
Perineural invasion	21 (21.6)	18 (18.8)	0.720
Vascular invasion	32 (33.0)	25 (26)	0.344
Positive circumferential resection margin[d]	0 (0)	0 (0)	–
pT stage			0.504
Tis/T1	18 (18.6)	12 (12.5)	
T2	20 (20.6)	20 (20.8)	
T3	32 (33.0)	29 (30.2)	
T4a	27 (27.8)	35 (36.5)	
pN stage			0.619
N0	61 (62.9)	65 (67.7)	
N1	28 (28.9)	22 (22.9)	
N1a	11 (11.3)	10 (10.4)	
N1b	13 (13.4)	10 (10.4)	
N1c	4 (4.1)	2 (2.1)	
N2	8 (8.2)	9 (9.4)	
N2a	6 (6.2)	8 (8.3)	
N2b	2 (2.1)	1 (1)	
pTNM stage			0.671
0	4 (4.1)	5 (5.2)	
I	28 (28.9)	24 (25.0)	
II	29 (29.9)	36 (37.5)	
IIA	17 (17.5)	18 (18.8)	
IIB	12 (12.4)	18 (18.8)	
III	36 (37.1)	31 (32.3)	
IIIA	6 (6.2)	1 (1)	
IIIB	25 (25.8)	26 (27.1)	
IIIC	5 (5.2)	4 (4.2)	

Values in parentheses are percentages unless indicated otherwise.
WD, well differentiated; MD, moderately differentiated; PD, poorly differentiated.
[a] *χ^2 or Fisher's exact test.*
[b] *Values are median (IQR).*
[c] *Mann–Whitney U test.*
[d] *Assessed in rectal cancer.*

In addition, the conversion rate of SILS (15.5%) was similar to previous RCT studies (9, 16–18) and the operation time did not increase, suggesting that SILS for selected patients performed by an experienced surgeon is short-term safe and feasible.

The SILS group showed lower VAS scores on POD1 and POD2 with similar postoperative analgesics usage in the present study, which may be related to fewer incisions. However, the recovery process in the SILS group did not speed up compared with the CLS group. Patient management greatly affects the postoperative recovery process. In the study of Osborne et al. (20), the patients received enhanced recovery after surgery (ERAS), and the postoperative hospital stay in the SILS group for high anterior resection was 1 day, which was faster than that in the CLS group (3 days).

Total incision length is commonly used to evaluate cosmetic effects. As reported above, the SILS group had a shorter incision length because of fewer trocars. However, cosmetic effect is a subjective feeling not only determined by the incision length. Some reported scales and questionnaires may be more suitable for the evaluation of cosmetic effect (21, 22). In addition, the informed consent process was very important for the description of the surgical scar site and size, which would directly affect the psychological recognition and acceptance of the incision (23).

In terms of long-term outcomes, only one RCT study (11) and a few retrospective studies (24–26) have been reported. These studies showed comparable 3- or 5-year survival rates in both groups. In addition, long-term follow-up is needed to determine whether SILS increases the incidence of incisional hernia. In the present trial, all patients are currently being followed up, and long-term outcomes will be reported when all study endpoints have been reached.

The inclusion and exclusion criteria of the current study were strict due to technical challenges associated with SILS. Indications of SILS for colorectal cancer still need to be explored. In the study of Jung et al. (27), among the 144 cases of LAR and 3 cases of APR, one additional trocar was needed in 107 cases because of the special complexity and difficulty on distal division with insufficient angled stapler and proper total mesorectal excision, which was considered as a second-string procedure. We argue that this result suggests that SILS may not be appropriate for rectal cancer with low tumor sites, and hence, these patients were excluded from the study.

At present, the development of SILS for colorectal cancer is mainly limited by the technical challenges, including loss of triangulation, parallel coaxial effect, poor exposure, and instrument collision. The unique skill sets cannot be directly adapted from existing conventional laparoscopic surgery experience (28). The internal instrument cross and external hand cross technique are the main methods to restore the triangulation. The introduction of 3D laparoscope and flexible laparoscope, reasonable position adjustment, and suspension technique can effectively expose the surgical field. In the future, with the integration of instrument functions and the application of robotic surgery, the difficulty of SILS will be hopefully further reduced.

This study has several limitations. First, the inclusion and exclusion criteria were very strict, especially that the exclusion criteria of BMI >30 kg/m^2 would exclude a large number of patients in more industrialized countries. Second, the SILS were all performed by the same senior surgeon, limiting the generalizability of the findings. Third, the protocol did not include ERAS protocols which have become routine at most institutions, so the assessment of postoperative recovery may not be entirely reliable.

CONCLUSIONS

Compared with CLS, SILS performed by experienced surgeons for selected colorectal cancer patients is non-inferior with good short-term safety and has the advantage of reducing postoperative pain.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Clinical Trial Ethics Committee of Ruijin Hospital (North). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

RZ, XJ, and TZ had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: RZ, ZS, KL, XJ, and TZ. Acquisition, analysis, or interpretation of data: all authors. Drafting of the manuscript: ZS, KL, YL, XJ, TZ, and RZ. Critical revision of the manuscript for important intellectual content: ZS, KL, YL, XJ, TZ, and RZ. Statistical analysis: ZS, KL, and YS. Obtained funding: RZ. Administrative, technical, or material support: all authors. Supervision: RZ, XJ, and TZ. All authors contributed to the article and approved the submitted version.

FUNDING

This study was supported by the Advanced and Appropriate Technology Promotion Projects of Shanghai Municipal Health Commission (2019SY058) and Clinical Skills and Innovations 3-Year Program of Shanghai Hospital Development Center (SHDC2020CR1026B).

REFERENCES

1. Lacy AM, García-Valdecasas JC, Delgado S, Castells A, Taurá P, Piqué JM, et al. Laparoscopy-Assisted Colectomy Versus Open Colectomy for Treatment of non-Metastatic Colon Cancer: A Randomised Trial. *Lancet* (2002) 359(9325):2224–9. doi: 10.1016/S0140-6736(02)09290-5
2. Veldkamp R, Kuhry E, Hop WC, Jeekel J, Kazemier G, Bonjer H, et al. Laparoscopic Surgery Versus Open Surgery for Colon Cancer: Short-Term Outcomes of a Randomised Trial. *Lancet Oncol* (2005) 6(7):477–84. doi: 10.1016/S1470-2045(05)70221-7
3. Guillou PJ, Quirke P, Thorpe H, Walker J, Jayne DG, Smith AM, et al. Short-Term Endpoints of Conventional Versus Laparoscopic-Assisted Surgery in Patients With Colorectal Cancer (MRC CLASICC Trial): Multicentre, Randomised Controlled Trial. *Lancet* (2005) 365(9472):1718–26. doi: 10.1016/S0140-6736(05)66545-2
4. Clinical Outcomes of Surgical Therapy Study Group, Nelson H, Sargent DJ, Wieand HS, Fleshman J, Anvari M, et al. A Comparison of Laparoscopically Assisted and Open Colectomy for Colon Cancer. *N Engl J Med* (2004) 350 (20):2050–9. doi: 10.1056/NEJMoa032651
5. Kang SB, Park JW, Jeong SY, Nam BH, Choi HS, Kim DW, et al. Open Versus Laparoscopic Surgery for Mid or Low Rectal Cancer After Neoadjuvant Chemoradiotherapy (COREAN Trial): Short-Term Outcomes of an Open-Label Randomised Controlled Trial. *Lancet Oncol* (2010) 11(7):637–45. doi: 10.1016/S1470-2045(10)70131-5
6. van der Pas MH, Haglind E, Cuesta MA, Fürst A, Lacy AM, Hop WC, et al. Laparoscopic Versus Open Surgery for Rectal Cancer (COLOR II): Short-Term Outcomes of a Randomised, Phase 3 Trial. *Lancet Oncol* (2013) 14 (3):210–8. doi: 10.1016/S1470-2045(13)70016-0
7. Bucher P, Pugin F, Morel P. Single Port Access Laparoscopic Right Hemicolectomy. *Int J Colorectal Dis* (2008) 23(10):1013–6. doi: 10.1007/s00384-008-0519-8
8. Cianchi F, Staderini F, Badii B. Single-Incision Laparoscopic Colorectal Surgery for Cancer: State of Art. *World J Gastroenterol* (2014) 20(20):6073–80. doi: 10.3748/wjg.v20.i20.6073
9. Lee YS, Kim JH, Kim HJ, Lee SC, Kang BM, Kim CW, et al. Short-Term Outcomes of Single-Port Versus Multiport Laparoscopic Surgery for Colon Cancer: The SIMPLE Multicenter Randomized Clinical Trial. *Ann Surg* (2021) 273(2):217–23. doi: 10.1097/SLA.0000000000003882
10. Athanasiou C, Pitt J, Malik A, Crabtree M, Markides GA. A Systematic Review and Meta-Analysis of Single-Incision Versus Multiport Laparoscopic Complete Mesocolic Excision Colectomy for Colon Cancer. *Surg Innov* (2020) 27(2):235–43. doi: 10.1177/1553350619893232
11. Watanabe J, Ishibe A, Suwa H, Ota M, Fujii S, Kubota K, et al. Long-Term Outcomes of a Randomized Controlled Trial of Single-Incision Versus Multi-Port Laparoscopic Colectomy for Colon Cancer. *Ann Surg* (2021) 273 (6):1060–165. doi: 10.1097/SLA.0000000000004252
12. Song Z, Li Y, Liu K, Jiang Y, Shi Y, Ji X, et al. Clinical and Oncologic Outcomes of Single-Incision Laparoscopic Surgery for Right Colon Cancer: A Propensity Score Matching Analysis. *Surg Endosc* (2019) 33(4):1117–23. doi: 10.1007/s00464-018-6370-2
13. Jiang Y, Song Z, Cheng X, Liu K, Shi Y, Wang C, et al. Clinical and Oncological Outcomes of Single-Incision vs. Conventional Laparoscopic Surgery for Rectal Cancer. *Surg Endosc* (2020) 34(12):5294–303. doi: 10.1007/s00464-019-07317-5
14. Poon JT, Cheung CW, Fan JK, Lo OS, Law WL. Single-Incision Versus Conventional Laparoscopic Colectomy for Colonic Neoplasm: A Randomized, Controlled Trial. *Surg Endosc* (2012) 26(10):2729–34. doi: 10.1007/s00464-012-2262-z11
15. Huscher CG, Mingoli A, Sgarzini G, Mereu A, Binda B, Brachini G, et al. Standard Laparoscopic Versus Single-Incision Laparoscopic Colectomy for Cancer: Early Results of a Randomized Prospective Study. *Am J Surg* (2012) 204(1):115–20. doi: 10.1016/j.amjsurg.2011.09.005
16. Bulut O, Aslak KK, Levic K, Nielsen CB, Rømer E, Sørensen S, et al. A Randomized Pilot Study on Single-Port Versus Conventional Laparoscopic Rectal Surgery: Effects on Postoperative Pain and the Stress Response to Surgery. *Tech Coloproctol* (2015) 19(1):11–22. doi: 10.1007/s10151-014-1237-6
17. Kang BM, Park SJ, Lee KY, Lee SH. Single-Port Laparoscopic Surgery Can Be Performed Safely and Appropriately for Colon Cancer: Short-Term Results of a Pilot Randomized Controlled Trial. *J Laparoendosc Adv Surg Tech A* (2017) 27(5):501–9. doi: 10.1089/lap.2016.0467
18. Watanabe J, Ota M, Fujii S, Suwa H, Ishibe A, Endo I. Randomized Clinical Trial of Single-Incision Versus Multiport Laparoscopic Colectomy. *Br J Surg* (2016) 103(10):1276–81. doi: 10.1002/bjs.10212
19. Maggiori L, Tuech JJ, Cotte E, Lelong B, Denost Q, Karoui M, et al. Single-Incision Laparoscopy Versus Multiport Laparoscopy for Colonic Surgery: A Multicenter, Double-Blinded, Randomized Controlled Trial. *Ann Surg* (2018) 268(5):740–6. doi: 10.1097/SLA.0000000000002836
20. Osborne AJ, Lim J, Gash KJ, Chaudhary B, Dixon AR. Comparison of Single-Incision Laparoscopic High Anterior Resection With Standard Laparoscopic High Anterior Resection. *Colorectal Dis* (2013) 15(3):329–33. doi: 10.1111/j.1463-1318.2012.03178.x
21. Dunker MS, Stiggelbout AM, van Hogezand RA, Ringers J, Griffioen G, Bemelman WA. Cosmesis and Body Image After Laparoscopic-Assisted and Open Ileocolic Resection for Crohn's Disease. *Surg Endosc* (1998) 12 (11):1334–40. doi: 10.1007/s004649900851
22. Lee SW, Milsom JW, Nash GM. Single-Incision Versus Multiport Laparoscopic Right and Hand-Assisted Left Colectomy: A Case-Matched Comparison. *Dis Colon Rectum* (2011) 54(11):1355–61. doi: 10.1097/DCR.0b013e31822c8d41

23. Bush AJ, Morris SN, Millham FH, Isaacson KB. Women's Preferences for Minimally Invasive Incisions. *J Minim Invasive Gynecol* (2011) 18(5):640–3. doi: 10.1016/j.jmig.2011.06.009
24. Yun JA, Yun SH, Park YA, Huh JW, Cho YB, Kim HC, et al. Oncologic Outcomes of Single-Incision Laparoscopic Surgery Compared With Conventional Laparoscopy for Colon Cancer. *Ann Surg* (2016) 263 (5):973–8. doi: 10.1097/SLA.0000000000001226
25. Miyo M, Takemasa I, Ishihara H, Hata T, Mizushima T, Ohno Y. Long-Term Outcomes of Single-Site Laparoscopic Colectomy With Complete Mesocolic Excision for Colon Cancer: Comparison With Conventional Multiport Laparoscopic Colectomy Using Propensity Score Matching. *Dis Colon Rectum* (2017) 60(7):664–73. doi: 10.1097/DCR.0000000000000810
26. Katsuno G, Fukunaga M, Nagakari K, Yoshikawa S, Azuma D, Kohama S. Short-Term and Long-Term Outcomes of Single-Incision Versus Multi-Incision Laparoscopic Resection for Colorectal Cancer: A Propensity-Score-Matched Analysis of 214 Cases. *Surg Endosc* (2016) 30(4):1317–25. doi: 10.1007/s00464-015-4371-y
27. Jung KU, Yun SH, Cho YB, Kim HC, Lee WY, Chun HK. The Role of Hand-Assisted Laparoscopic Technique in the Age of Single-Incision Laparoscopy: An Effective Alternative to Avoid Open Conversion in Colorectal Surgery. *J Laparoendosc Adv Surg Tech A* (2018) 28(4):415–21. doi: 10.1089/lap.2017.0553
28. Pucher PH, Sodergren MH, Singh P, Darzi A, Parakseva P. Have We Learned From Lessons of the Past? A Systematic Review of Training for Single Incision Laparoscopic Surgery. *Surg Endosc* (2013) 27(5):1478–84. doi: 10.1007/s00464-012-2632-6

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Surgery

ORIGINAL RESEARCH
published: 08 November 2021
doi: 10.3389/fsurg.2021.745875

Plasma Levels of Keratinocyte Growth Factor Are Significantly Elevated for 5 Weeks After Minimally Invasive Colorectal Resection Which May Promote Cancer Recurrence and Metastasis

H. M. C. Shantha Kumara[1†], Abhinit Shah[1†], Hiromichi Miyagaki[2†], Xiaohong Yan[1†], Vesna Cekic[1†], Yanni Hedjar[1†] and Richard L. Whelan[1,3†]*

[1] Division of Colon and Rectal Surgery, Department of Surgery, Lenox Hill Hospital, Northwell Health, New York, NY, United States, [2] Gastroenterological Surgery, Osaka University, Suita, Japan, [3] Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY, United States

Background: Human Keratinocyte Growth Factor (KGF) is an FGF family protein produced by mesenchymal cells. KGF promotes epithelial cell proliferation, plays a role in wound healing and may also support tumor growth. It is expressed by some colorectal cancers (CRC). Surgery's impact on KGF levels is unknown. This study's purpose was to assess plasma KGF levels before and after minimally invasive colorectal resection (MICR) for CRC.

Aim: To determine plasma KGF levels before and after minimally invasive colorectal resection surgery for cancer pathology.

Method: CRC MICR patients (pts) in an IRB approved data/plasma bank were studied. Pre-operative (pre-op) and post-operative (post-op) plasma samples were taken/stored. Late samples were bundled into 7 day blocks and considered as single time points. KGF levels (pg/ml) were measured *via* ELISA (mean ± SD). The Wilcoxon paired *t*-test was used for statistical analysis.

Results: Eighty MICR CRC patients (colon 61%; rectal 39%; mean age 65.8 ± 13.3) were studied. The mean incision length was 8.37 ± 3.9 and mean LOS 6.5 ± 2.6 days. The cancer stage breakdown was; I (23), II (26), III (27), and IV (4). The median pre-op KGF level was 17.1 (95 %CI: 14.6–19.4; $n = 80$); significantly elevated ($p < 0.05$) median levels (pg/ml) were noted on post-op day (POD) 1 (23.4 pg/ml; 95% CI: 21.4–25.9; $n = 80$), POD 3 (22.5 pg/ml; 95% CI: 20.7–25.9; $n = 76$), POD 7–13 (21.8 pg/ml; 95% CI: 17.7–25.4; $n = 50$), POD 14–20 (20.1 pg/ml; 95% CI: 17.1–23.9; $n = 33$), POD 21–27 (19.6 pg/ml; 95% CI: 15.2–24.9; $n = 15$) and on POD 28–34 (16.7 pg/ml; 95% CI: 14.0–25.8; $n = 12$).

OPEN ACCESS

Edited by:
Ren Zhao,
Shanghai Jiao Tong University, China

Reviewed by:
Beatrice Aramini,
University Hospital of Modena, Italy
Vivien Koh,
National University Health System, Singapore

***Correspondence:**
Richard L. Whelan
rwhelan1@northwell.edu

†ORCID:
H. M. C. Shantha Kumara
orcid.org/0000-0002-3740-2201
Abhinit Shah
orcid.org/0000-0002-1627-1337
Hiromichi Miyagaki
orcid.org/0000-0001-8106-330X
Xiaohong Yan
orcid.org/0000-0001-8116-1161
Vesna Cekic
orcid.org/0000-0002-8130-6540
Yanni Hedjar
orcid.org/0000-0002-1556-2837
Richard L. Whelan
orcid.org/0000-0002-9707-4967

Specialty section:
This article was submitted to Surgical Oncology, a section of the journal Frontiers in Surgery

Received: 22 July 2021
Accepted: 08 October 2021
Published: 08 November 2021

Citation:
Shantha Kumara HMC, Shah A, Miyagaki H, Yan X, Cekic V, Hedjar Y and Whelan RL (2021) Plasma Levels of Keratinocyte Growth Factor Are Significantly Elevated for 5 Weeks After Minimally Invasive Colorectal Resection Which May Promote Cancer Recurrence and Metastasis. Front. Surg. 8:745875. doi: 10.3389/fsurg.2021.745875

Conclusion: Plasma KGF levels were significantly elevated for 5 weeks after MICR for CRC. The etiology of these changes is unclear, surgical trauma related acute inflammatory response and wound healing process may play a role. These changes, may stimulate angiogenesis in residual tumor deposits after surgery.

Keywords: minimally invasive colorectal resection, KGF, plasma levels, metastasis, angiogenesis

INTRODUCTION

Surgery remains the mainstay of treatment for colon and rectal cancer (CRC). Unfortunately, 30–40% of patients who undergo "curative" resection harbor micrometastases after surgery that lead to tumor recurrences. Neoadjuvant and adjuvant chemotherapy, radiotherapy and immunotherapy have improved survival, however, despite these treatments a good proportion of patients eventually succumb (1–3). Interestingly, surgery, necessary to remove the primary tumor, may transiently create an environment, *via* immunosuppression or other surgery related alterations, that is conducive to the growth of residual cancer microfoci or circulating viable tumor cells (4–6). There is clinical and murine evidence of accelerated tumor growth early after surgery that supports this hypothesis (4, 7–9). If a tumor supportive milieu exists after surgery then it is logical to develop anti-cancer treatments for use during the first 4–6 weeks after surgery which is a time period not currently being utilized (10, 11). One proposed mechanism for accelerated tumor development after surgery are long duration proangiogenic and tumor stimulatory plasma protein changes that may stimulate tumor growth in residual tumor microfoci.

The vast majority of plasma protein changes after surgery last hours or days (IL-1, TNF, IL-6, CRP, etc.) (12–14), however, in the last decade, increases in blood levels of at least 12 progangiogenic proteins have been noted to persist for 3 to 5 weeks after resection of colorectal cancer (CRC) (15–25). *In vitro* studies utilizing endothelial cells (EC's), critical to angiogenesis, suggest the net effect of plasma compositional changes is proangiogenic. Plasma from the 2nd and 3rd weeks after minimally invasive colorectal cancer resection (MICR) stimulates endothelial cell (EC) proliferation, invasion and migration which are required for neovascularization (15, 26). The principal source of the added protein in the blood is thought to be the healing surgical wounds (27). Efforts to further characterize the surgery-related plasma protein changes continue. Keratinocyte Growth Factor (KGF) is a good candidate for study because it is involved with wound healing and also impacts epithelial cell growth.

KGF, also known as FGF-7, is a member of the Fibroblast Growth Factor family. It is involved in a variety of biological processes, including cell growth, morphogenesis and tissue repair. It is generated by fibroblasts and other mesenchymal cells and works exclusively through the FGFR2b and FGFR2c receptors that are expressed mainly by epithelial cells (28, 29). KGF's effects are largely paracrine since it effects epithelium and, therefore, it is a mediator of mesenchymal-epithelial interactions (30, 31). KGF expression is stimulated by IL1 and IL6 (28, 29, 32) as well as by platelet-derived growth factor BB (PDGF BB) and transforming growth factor α (TGFα). KGF is induced in the setting of both acute and chronic injury and there is also strong evidence that KGF plays an role in wound healing (33, 34).

The binding of fibroblast derived KGF to KGFR on epithelial cells promotes re-epithelialization after injury. Exogenous KGF facilitates both skin wound and anastomotic healing in rodents and mice (35–37). Wound healing is impaired in KGF knockout mice and after KGF blockade (36). There is also evidence that KGF impacts wound angiogenesis (36, 38, 39). Diminished angiogenesis and lower VEGF levels been noted in wounds of KGF knockout mice (vs. wild type mice) (36). Given its role in epithelial wound healing it is not surprising that KGF impacts cancer growth as well.

KGF has been shown to facilitate the growth of KGFR expressing epithelial cancers. Stomach, colon, pancreas, ovarian, and other cancers have been shown to express this receptor (40–44). Although the peri-tumor stroma is the principal source of KGF, some tumor cells also express this protein (42, 45–47). KGF has been shown to be a tumor cell mitogen and to promote cancer cell motility, VEGF production, and tumor angiogenesis (41, 43, 47, 48).

Given KGF's role in cancer development and the hypothesis that proteins with long duration plasma elevations after surgery originate in the wound, it is logical to perform an in depth perioperative plasma study for KGF in patients with CRC. Surgery's impact on KGF levels is not well-documented. The purpose of this study was to determine pre-operative (pre-op) and post-operative plasma KGF levels for 5 weeks after minimally invasive resection (MICR) of CRC.

METHODS

Study Population

Colorectal cancer (CRC) patients who underwent elective minimally invasive colorectal resection (MICR) at Mount Sinai West Hospital and New York Presbyterian Hospital between 2006 and 2013 who had been enrolled in an IRB approved multicenter prospective tissue and data bank (Institutional Review Board of the Mount Sinai School of Medicine, New York; IRB Reference No: GCO1: 16-2619 and Institutional Review Board of the Columbia University Medical Center, New York; IRB Reference No: AAAA4473) were eligible for the present study. The generally stated purpose of the tissue and data bank was to study the physiologic, immunologic, and oncologic ramifications of major abdominal surgery. Enrolled patients underwent minimally invasive laparoscopic-assisted (LAP) or hand assisted laparoscopic (HAL) surgery; none of the patients received a novel drug or other therapy. The indications and type of surgery as well as the demographic, operative, and short-term recovery data were prospectively collected for all the patients. Intraoperative or recently transfused patients, immunosuppressed patients (medication-related and HIV+), and those who received radio- or chemotherapy within 6 weeks of surgery were excluded. Patients undergoing urgent or emergent surgery were also excluded. Clinical, demographic, and operative data were obtained from office charts as well as operative and pathology records.

Blood Sampling and Processing

As per the tissue banking protocol, research dedicated blood samples were obtained from consenting CRC MICR patients pre-operatively, on post-operative days (POD) 1, 3, and at different time points beyond the first week following surgery. Only those patients for whom adequate volumes of plasma were available for the pre-op, POD 1, POD 3, and at least 1 late time point were enrolled. Since post-discharge blood samples were taken at the time of follow-up office visits which varied considerably as to the specific post-operative day they occurred, it was necessary to "bundle" the late samples into 7 day time blocks (POD 7–13, POD 14–20, POD 21–27, and POD 28–34). Specimens from these 7 day periods were considered as single time points. The post-operative time blocks were made based on the time of samples collection. Of note, the "*n*" for each of the post-hospital discharge time points is well less than the starting "*n*" of 80 because patients were generally seen only 1 to 2 times during the first 5 weeks following surgery (and not on a weekly basis). Specimens were collected in heparin-containing tubes, and processed within 5–6 h of collection. After centrifugation at 450 × g for 10 min, the plasma was frozen and stored at −80°C until the assays were performed.

Plasma KGF Analysis

Blood samples were obtained pre-operatively, at POD 1 or POD 3, and at least one late time point (POD 7–34) into heparin-containing blood collection tubes and processed within 5–6 h. The plasma samples were isolated *via* centrifugation (450XG for 10 min at 6°C) and stored in 500 ul aliquots. Plasma KGF levels were analyzed in duplicate using a commercially available enzyme-linked immunosorbent assay (R and D Systems, Minneapolis, MN, USA) according to the manufacturer's instructions. Briefly, 100 μL plasma samples in duplicate were used for the assay. The human KGF standard stock solution (20,000 pg/mL) was made with deionized water by reconstituting ELISA kit accompanied standard. Samples were prepared for analysis following the KGF assay kit (Catalog Number DKG00) protocol provided with the kit. A standard curve for each plate was made by using dilution series of KGF standard stock solution where the 2000 pg/mL standard serves as the high standard. The calibrator diluent serves as the zero standards (0 pg/mL). The optical density of ELISA plate was determined at the end of the reaction using an automated microplate reader (Synergy2; Bio-Tek Instruments, Inc., Winooski, VT, USA) set to 450 nm and plasma KGF concentrations were determined using the standard curve. The standard curve was created using software capable of generating a log/log curve-fit and protein concentrations are reported as pg/ml.

Statistical Analysis

Demographic and clinical data are expressed as the mean ± SD for continuous variables. In the analysis of pre-op vs. post-op KGF levels in CRC patients, the Wilcoxon signed rank test was used for analysis. To exhibit significant differences between Pre-op vs. post-op values the data is depicted in a bar graph expressing KGF levels as median and 75% quartile range. Since the "*n*" at the later timepoints varies and progressively decreases, a unique pre-op results bar that depicts the median values is included for each timepoint. Comparisons of KGF levels of male vs. female patients and hand-assisted vs. laparoscopic patients were carried out using the Mann Whitney test. Correlation between post-op plasma KGF levels and age, incision size and length of surgery was assessed by the Spearman's rank correlation coefficient (rs). Data analysis was performed using SPSS version 15.0 (SPSS, Inc., Chicago, IL, USA).

RESULTS

A total of 80 CRC patients (37 males, 43 females; mean age 65.8 ± 13.3 years) who underwent MICR were included in the study. Of the 80 patients, 49 patients (61%) had colon cancer, while 31 patients (39%) had rectal malignancies. Of note, the colon cancer subgroup was significantly older than the rectal cancer cohort (68.2 ± 12.5 vs. 62.1 ± 14.1). The majority of patients underwent laparoscopic-assisted resection (58%), whereas the remainder (42%) underwent a hand-assisted or hybrid laparoscopic procedure. The breakdown of operations performed was as follows: Right colectomy, 34%; LAR/anterior resection, 24%; sigmoid/rectosigmoid, 21%; subtotal/total colectomy, 9%; transverse colectomy, 6%, left colectomy, 4%; and APR, 2% (**Table 1**). The mean incision length was 5.9 ± 1.9 cm for LAP and 10.97 ± 3.3 cm for HAL, and the mean length of stay was 6.5 ± 2.6 days. The final cancer stage breakdown was as follows: Stage I (23); Stage II (27); Stage III (26); and Stage IV (4). There were no perioperative deaths and there were no superficial, deep, or organ space surgical site infections noted. Eleven post-operative complications were noted and included: ileus (5), urinary tract infection (3), C-Diff colitis (1), phlebitis (1), and seroma (1).

The median pre-op KGF level was 17.1 pg/ml (95%CI: 14.6–19.4; $n = 80$). When compared to pre-op levels, significant elevations in the median plasma KGF level (pg/ml) were identified at all 5 post-op time points: POD 1 (23.4 pg/ml; 95% CI: 21.4–25.9; $n = 80$, $p < 0.0001$), POD 3 (22.5 pg/ml; 95% CI: 20.7–25.9; $n = 76$, $p < 0.0001$), POD 7–13 (21.8 pg/ml; 95% CI: 17.7–25.4; $n = 50$, $p < 0.0001$), POD 14–20 (20.1 pg/ml;95% CI: 17.1–23.9; $n = 33$, $p < 0.0001$), POD 21–27 (19.6 pg/ml; 95% CI: 15.2–24.9; $n = 15$, $p = 0.03$) and on POD 28–34 (16.7 pg/ml; 95% CI: 14.0–25.8; $n = 12$, $p = 0.001$) (**Figure 1**). The percent increase from median baseline at each time point was 36.9% at POD 1, 31.8%; at POD 3, 26.8%; at POD 7–13, 29.7%; at POD 14–20, 14.1%; at POD 21–27, and 38.7% at POD 28–34. Of note, because the *n*'s for 5 of the 6 post-op time points vary, the mean

TABLE 1 | Demographic and clinical characteristics of the study population.

Age, years (mean ± SD)	65.8 ± 13.3
Sex (*n*):	
Male	37 (46.0%)
Female	43 (54.0%)
Incision length (entire patient population), cm (mean ± SD)	8.37 ± 3.9
Incision length (lap procedure group), cm (mean ± SD)	5.91 ± 1.9
Incision length (hand procedure group), cm (mean ± SD)	10.97 ± 3.3
Operative time, min (mean ± SD)	295.0 ± 129.9
Length of stay, days (mean ± SD)	6.5 ± 2.6
Pathological stage (*n*)	
Stage I	23 (29%)
Stage II	27 (34%)
Stage III	26 (32%)
Stage IV	4 (5%)
Type of resection (*n*):	
Right	27 (34.0%)
LAR/AR (16/3)	19 (24.0%)
Sigmoid /recto-sigmoid (14/3)	17 (21.0%)
Total/sub total (3/3)	6 (9.0%)
Transverse	5 (6.0%)
Left	3 (4.0%)
APR	2 (2.0%)
Surgical method:	
Laparoscopic-assisted (LAP)	46 (58.0%)
Hand-assisted/hybrid laparoscopic (HAL)	34 (42.0%)

pre-op value at these time points differs. Thus, as regards the figure displaying the results, there are two bars shown for each time point (left bar depicts the pre-op result and the right the post-op result).

No significant differences in post-operative KGF levels were noted in relation to sex, incision length, or the surgical method. Similarly, post-op KGF levels did not correlate with cancer stage. Of note, when each time point's results were considered independently, age directly correlated with KGF levels pre-operatively and at 3 of the 6 post-op time points. Also, the colon cancer subgroup had higher mean KGF levels at 5 of the 6 post-op time points although significance was reached only on POD 1. Finally, the operative length of surgery directly correlated with the mean KGF level at 1 of the 6 post-operative time points (POD 1).

DISCUSSION

This study of perioperative plasma KGF levels in the setting of MICR assessed 6 post-operative timepoints and revealed that blood levels are significantly elevated over pre-operative baseline for 5 weeks after surgery. As regards mean KGF values, the percent change from pre-op baseline ranged from 26.8 to 38.7% at 5 of the 6 time points. There was no association found between post-operative KGF levels and sex, length of incision, surgical method, or the final cancer stage. When each post-op time point's results were considered alone, KGF levels correlated directly with age pre-operatively and at 3 of 6 post-op timepoints. Also, the colon cancer subgroup, significantly older than the rectal cancer cohort, had significantly higher mean post-op KGF levels than the rectal cancer group at 1 of 6 time points (POD 1). Finally, the length of surgery directly correlated with the mean KGF level at 1 of the 6 post-operative timepoints. Thus, age, cancer location, and length of surgery may influence blood KGF levels.

The majority of plasma protein changes after surgery persist hours or days (12–25), however, in the last decade, increases in the blood levels of at least 12 proangiogenic proteins have been noted to persist for 3–5 weeks after resection of colorectal cancer (CRC). Included on this list are vascular endothelial growth factor (VEGF), angiopoeitin-2 (Ang-2), placental growth factor (PIGF), soluble vascular adhesion molecule-1 (sVCAM-1), Angiopoietin like 4 (ANPTL4), monocyte chemotactic protein-1 (MCP-1), human chitinase 3-like 1 (Chi3L1), matrix metalloproteinase-2(MMP-2),matrix metalloproteinase-3 (MMP-3), matrix metalloproteinase-3 (MMP-7), Chemokine (C-X-C motif) ligand 16 (CXCL 16), and Interleukin 8 (IL-8).

VEGF is a key promoter of several early steps in angiogenesis. Specifically, VEGF stimulates endothelial cell (EC) proliferation, microtubule formation, migration, and invasion supporting microvasculature development whereas Ang-2 destabilizes the connections between endothelium and perivascular cells, which enhance VEGFs effects (15). While stimulating EC proliferation and survival, PlGF recruits smooth muscle precursors that envelop developing vessels in tumors and together with VEGF produces more stable and mature vessels (17). It has been shown that the binding of sVCAM-1 to EC bound VLA4, *in vitro*, induces EC chemotaxis *via* the p38 mitogen-activated protein (MAP) kinase and focal adhesion kinase (FAK) signaling pathway which are important early step in the complex process of angiogenesis (18, 49, 50). MCP-1 is thought to facilitate angiogenesis *via* recruitment of proangiogenic protein producing monocytes and macrophages and endothelial cells into wounds and tumors (19). Macrophages in tumor stroma have been shown to express CHi3L1 which is likely to stimulate tumor angiogenesis (20, 51). MMP-2 ECM degradation releases VEGF and transforming growth factor β (TGF-β) and transformation of TGF-β into its active form is further supported by MMP-7 (25, 52–54). MMP-2, MMP-3 and MMP-7, as a proteases and regulator of cell matrix interactions, have been proposed to play a role in angiogenesis by paving the way for budding vessels and migrating cells (22, 55). CXCL16 is express on leukocytes, endothelial cells, and other tissues and its receptor CXCL6 found on cells at sites of inflammation (24). Endothelial precursor cell recruitment and angiogenesis induced by pro-inflammatory stimuli are thought to be associated with transmembrane chemokine CXCL16 and CXCR6 pair activity (56–58). IL-8 plays a role in angiogenesis as well as keratinocyte chemotaxis especially at the healing surgical wounds tissues (21). *In vitro* studies utilizing endothelial cells suggest the net effect of plasma compositional changes during 2nd and 3rd week post-operative period is proangiogenic. KGF joins the ranks of these 12 proteins

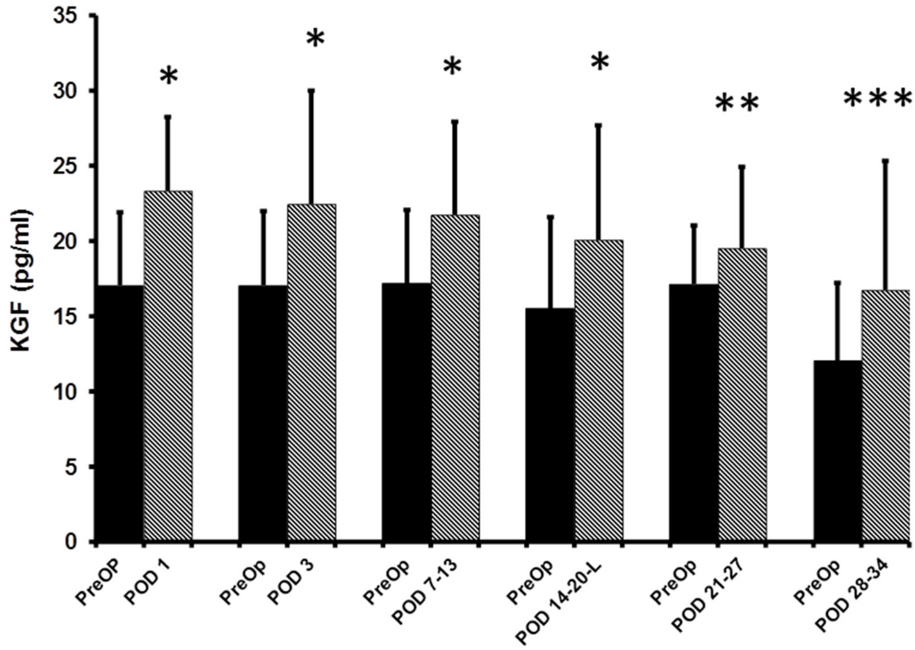


FIGURE 1 | ELISA determined pre-operative (Pre-op) and post-operative plasma KGF levels of colorectal cancer patients. KGF levels are expressed as median and 75% quartile range. *****Pre-op vs. POD 1 ($n = 80$, $p < 0.0001$); *****Pre-op vs. POD 3 ($n = 76$, $p < 0.0001$); *****Pre-op vs. POD 7-13 ($n = 50$, $p < 0.0001$); *Pre-op vs. POD 14–20 ($n = 33$, $p < 0.0001$); ******Pre-op vs. POD 21–27 (*n*-15, $p = 0.03$); *******POD 28–34 time point ($n = 12$, $p = 0.001$).

whose blood levels have been shown to be elevated after MICR. As noted, among numerous other effects, these proteins all play some role in angiogenesis; KGF shares that characteristics.

Niu et al. has noted in *in vitro* studies of pancreatic ductal cells, that the binding of KGF to its receptor induces NF Kappa B activation and leads to downstream activation of a cascade of target genes that, in turn, lead to the production and release of Matrix Metalloproteinase 9 (MMP-9), Vascular Endothelial Growth Factor (VEGF) and Urokinase-type Plasminogen Activator (u-PA). These factors then induce EC proliferation and migration which leads to the branching of micro vessels and neovascularization; MMP-9 and u-PA also facilitate cell migration and invasion (32). In several studies, KGF was shown to induce neovascularization in the rat cornea, and in an *in vitro* culture study of EC's obtained from small vessels it was demonstrated that KGF induced chemotaxis, stimulated EC proliferation, activated MAPK, and helped maintain the barrier function of EC's (38, 59). These proangiogenic effects are thought to promote both wound and tumor neovascularization (48). As mentioned, KGF has also been shown to promote tumor growth.

There is considerable evidence that KGF, in the setting of KGFR expressing tumors, promotes cancer development in multiple ways including stimulation of tumor cell proliferation, motility and/or invasion (27, 30, 32, 38, 40, 60). As mentioned, numerous epithelial cancers have been shown to express KGFR including colorectal, pancreatic, gastric, and ovarian cancer (40, 42, 44, 46, 48, 60–63). The source of the KGF, in most cancers, is the peri-tumor stroma although some tumors express this protein. Numerous mechanisms have been proposed to account for KGF's tumor promoting effects. In several colon cancer studies, KGF was shown to facilitate tumor cell proliferation *via* cyclin D, an essential regulator of cell cycle progression (64, 65). Having discussed KGF's potential impact on cancers, what is the etiology of these changes after surgery?

As mentioned, the cytokines IL-1 and 6 are known to induce KGF secretion, therefore, the elevation noted during the first few days following surgery may be a consequence of the acute inflammatory response. Beyond that point, since KGF plays a role in re-epithelialization and wound angiogenesis, the healing surgical wounds may be the source of the additional protein in the circulation. KGF may follow the concentration gradient from the wound (high KGF levels) to the circulation (low KGF levels). This is in keeping with many of the other proteins, mentioned above, whose plasma levels have been shown to be persistently increased after colorectal resection (11, 15, 16, 18, 19, 21–26). In a study that simultaneously assessed plasma and wound fluid levels of 8 of these "long duration" proteins after colorectal resection, it was demonstrated that the mean wound levels of the proteins were 3 to 40 times higher than their corresponding plasma concentrations which, in turn, were significantly elevated from their pre-operative baseline blood levels (27). As noted, KGF, in addition to having proangiogenic effects, also plays a role in the wound healing process.

Although low levels of KGF are found in normal epithelium, studies have shown that notably higher levels of KGF mRNA and protein are noted along the advancing edge of wounds during re-epithelialization (66). KGF, generated by fibroblasts

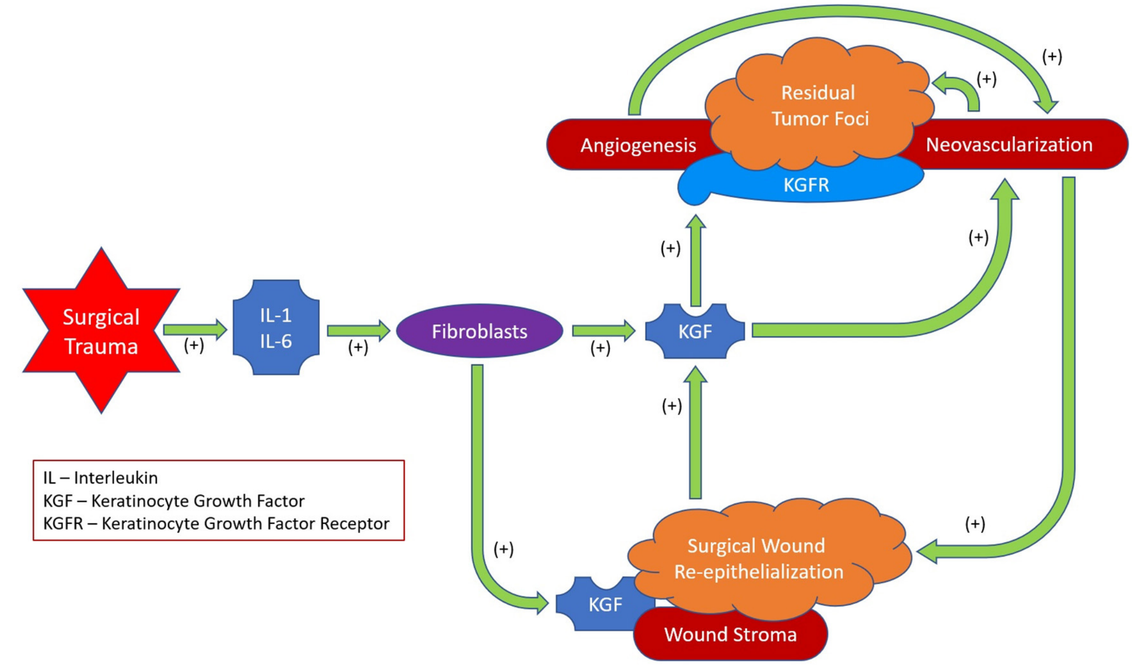


FIGURE 2 | Proposed ramifications of surgical trauma related plasma KGF effects.

and other mesenchymal cells in the wound stroma, impacts KGFR expressing keratinocytes and a wide variety of epithelial cells (39, 67, 68). As noted, KGF promotes epithelial cell proliferation, differentiation, migration and has also been shown to promote wound contraction in a rodent model of diabetic wounds (27, 28). What are the potential clinical implications of the post-operative KGF changes?

In theory, a month long period of elevated plasma KGF levels might stimulate the growth of residual cancer deposits after resection of the primary tumor. This idea seems more reasonable when considered in light of the other 12 proteins whose blood levels are similarly elevated for 3–5 weeks. As regards neovascularization, the collective effect of the surgery-related plasma compositional changes is to stimulate EC proliferation, mobility, and invasion when compared to pre-operative plasma (15, 26). Thus, tumor angiogenesis may be stimulated post-operatively. The authors also believe that the long duration plasma protein changes, including the KGF elevations, may promote tumor development by directly stimulating tumor cell mitosis, mobility, and growth *via* multiple mechanisms including the inhibition of apoptosis (69–71). All of the proteins that are persistently elevated after CRC have been shown to promote tumor growth in numerous ways in addition to having proangiogenic effects. When considered in light of existing concerns regarding the possible tumor promoting effects of surgery, the development of anti-tumor treatments and strategies that can be employed perioperatively is logical.

Presently, for the vast majority of solid cancers for whom the primary treatment is surgical resection, the perioperative time period is not used for any anticancer treatment. Potential therapies that have been proposed for use in the perioperative period in either the murine or clinical setting include immunomodulation (FLT-3, GMCSF,), tumor vaccines, monoclonal antibodies to EGFR, H-2 blockers (shown to inhibit some regulatory T cells), and anti-oxidants with anti-tumor effects such as EGCG (green tea component) and siliphos (milk thistle component) (10, 11, 72–74). Clearly, more research in this area is warranted.

In conclusion, after MICR for CRC, plasma KGF levels are significantly elevated over baseline levels for 5 weeks. The etiology of these post-operative changes was not assessed in this study. However the cytokines IL-1 and IL6 are known to induce KGF secretion, therefore, the elevation noted during the first few days following surgery may be a consequence of the acute inflammatory response. Beyond that point, since KGF plays a role in re-epithelialization and wound angiogenesis, the healing surgical wounds may be the source of the additional protein in the circulation (75–78). KGF may follow the concentration gradient from the wound (high KGF levels) to the circulation (low KGF levels). The clinical importance of these findings, if any, is unclear. Because KGF's purported effects include promotion of cell turnover, mobility, and angiogenesis, during the first post-op month residual KGFR expressing tumor deposits may be stimulated to grow (**Figure 2**).

Weaknesses of this study include a diminishing "*n*" and the need to "bundle" specimens for the final 4 post-hospital discharge time points. In defense, outpatient weekly blood draws are not feasible and it is not possible to coordinate late sampling so that it occurs on set days. Another shortcoming is that this study includes perioperative plasma data only. Ideally, tumor expression levels of KGFR and KGF would be determined as well. A correlative tumor expression study was not conducted due to the fact that we did not have an adequate number of tumor and normal tissue samples for the patients in this study. Also, in addition to assessing CRC patients who had minimally invasive surgery, ideally, patients undergoing "open" (large incision) surgery would also have been studied. Unfortunately, our bank has very few open surgery plasma samples because the great majority of cases are done using MIS methods. In addition, the study is too small to definitively determine the role that age, tumor location, tumor stage and length of surgery have on post-op KGF levels. Further studies with a larger study group would better answer these questions.

SUMMARY

After MICR for CRC, plasma KGF levels are significantly elevated over baseline levels for 5 weeks. The percent change from baseline was >25% for 5 of the 6 post-op time points. No correlation between KGF levels and tumor stage, surgical technique or sex was found, however, age >60 was associated with higher levels at some time points. KGF joins a group of 12 other proteins whose levels are persistently increased after MICR. The clinical import of these findings, if any, is unclear. Because KGF's purported effects include promotion of cell turnover, mobility, and angiogenesis, during the first post-op month residual KGFR expressing tumor deposits may be stimulated to grow. Further studies of the ramifications of surgery as regards plasma protein composition are warranted as is a search for anti-cancer agents suitable for use in the perioperative period.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because all data use for the research are included in the article. Other patients information data cannot be provided as per the IRB regulations. Requests to access the datasets should be directed to rwhelan1@northwell.edu.

ETHICS STATEMENT

The present study was conducted using material collected from patients who have consented to pre-operatively to participate in the Mount Sinai West Colorectal service's IRB approved general tissue and data banking protocol (Institutional Review Board of the Mount Sinai School of Medicine, New York NY; IRB Reference NO: GCO#1: 16-2619). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

HMCSK contributed to the conception, design, sample processing, statistical analysis, interpretation of data, and revision of the articles. HM and XY contributed to collection of human material clinical data and revision of the article. VC contributed to human sample collection, processing, analysis, and interpretation of data. AS and YH contributed to manuscript writing, interpretation of data, and revision of the articles. RW contributed to the conception, design, interpretation of data, and critical revision of the article. All authors drafted the article, made critical revisions, and approved the submitted final version of the article to be published.

FUNDING

This study was supported by a generous donation from the Wade Thompson Foundation to the Division of Colon and Rectal Surgery, Department of Surgery, Mount Sinai West Hospital (Grant account no: SL55002012), New York.

REFERENCES

1. Jagoditsch M, Lisborg PH, Jatzko GR, Wette V, Kropfitsch G, Denk H, et al. Long-term prognosis for colon cancer related to consistent radical surgery: multivariate analysis of clinical, surgical, and pathologic variables. *World J Surg.* (2000) 24:1264–70. doi: 10.1007/s002680010252
2. Aguiar Junior S, Oliveira MM, Silva DRME, Mello CAL, Calsavara VF, Curado MP. Survival of patients with colorectal cancer in a cancer center. Survival of patients with colorectal cancer in a cancer center. *Arq Gastroenterol.* (2020) 57:172–7. doi: 10.1590/s0004-2803.202000000-32
3. Bird NC, Mangnall D, Majeed AW. Biology of colorectal liver metastases: a review. *J Surg Oncol.* (2006) 94:68–80. doi: 10.1002/jso.20558
4. Peeters CF, Westphal JR, de Waal RM, Ruiter DJ, Wobbes T, Ruers TJ. Vascular density in colorectal liver metastases increases after removal of the primary tumor in human cancer patients. *Int J Cancer.* (2004) 112:554–9. doi: 10.1002/ijc.20374
5. Coffey JC, Wang JH, Smith MJ, Bouchier-Hayes D, Cotter TG, Redmond HP. Excisional surgery for cancer cure: therapy at a cost. *Lancet Oncol.* (2003) 4:760–8. doi: 10.1016/S1470-2045(03)01282-8
6. Slesser AA, Khan F, Chau I, Khan AZ, Mudan S, Tekkis PP, et al. The effect of a primary tumour resection on the progression of synchronous colorectal liver metastases: an exploratory study. *Eur J Surg Oncol.* (2015) 41:484–92. doi: 10.1016/j.ejso.2014.12.009
7. O'Reilly MS, Holmgren L, Shing Y, Chen C, Rosenthal RA, Moses M, et al. Angiostatin: a novel angiogenesis inhibitor that mediates the suppression of metastases by a Lewis lung carcinoma. *Cell.* (1994) 79:315–28. doi: 10.1016/0092-8674(94)90200-3
8. Fisher B, Gunduz N, Coyle J, Rudock C, Saffer E. Presence of a growth-stimulating factor in serum following primary tumor removal in mice. *Cancer Res.* (1989) 49:1996–2001.
9. Fisher B, Gunduz N, Saffer EA. Influence of the interval between primary tumor removal and chemotherapy on kinetics and growth of metastases. *Cancer Res.* (1983) 43:1488–92.
10. Wildbrett P, Oh A, Carter JJ, Schuster H, Bessler M, Jaboci CA Et al.Increased rates of pulmonary metastases following sham laparotomy compared to CO_2 pneumoperitoneum and the inhibition of metastases utilizing perioperative immunomodulation and a tumor vaccine. *Surg Endosc.* (2002) 16:1162–9. doi: 10.1007/s00464-001-8158-y
11. Kirman I, Maydelman A, Asi Z, Whelan RL. Effect of surgical trauma on epithelial cell adhesion molecule (GA-733) vaccine-induced tumor resistance. *Surg Endosc.* (2003) 17:505–9. doi: 10.1007/s00464-002-8862-2
12. Shantha Kumara HM, Tohme ST, Kim IY, Kim DG, Kalady MF, Luchtefeld M, et al. Minimally invasive colorectal resection is associated with a transient increase in plasma hepatocyte growth factor levels early after surgery for colon cancer. *Surg Innov.* (2011) 18:254–8. doi: 10.1177/1553350611399588

13. Harmon GD, Senagore AJ, Kilbride MJ, Warzynski MJ. Interleukin-6 response to laparoscopic and open colectomy. *Dis Colon Rectum.* (1994) 37:754–9. doi: 10.1007/BF02050137
14. Ordemann J, Jacobi CA, Schwenk W, Stösslein R, Müller JM. Cellular and humoral inflammatory response after laparoscopic and conventional colorectal resections. *Surg Endosc.* (2001) 15:600–8. doi: 10.1007/s004640090032
15. Kumara HM, Feingold D, Kalady M, Dujovny N, Senagore A, Hyman N, et al. Colorectal resection is associated with persistent proangiogenic plasma protein changes: postoperative plasma stimulates *in vitro* endothelial cell growth, migration, and invasion. *Ann Surg.* (2009) 249:973–7. doi: 10.1097/SLA.0b013e3181a6cd72
16. Belizon A, Balik E, Horst P, Feingold D, Arnell T, Azarani T. et al.Persistent elevation of plasma vascular endothelial growth factor levels during the first month after minimally invasive colorectal resection. *Surg Endosc.* (2008) 22:287–97. doi: 10.1007/s00464-007-9725-7
17. Shantha Kumara HM, Cabot JC, Yan X, Herath SA, Luchtefeld M, Kalady MF, et al. Minimally invasive colon resection is associated with a persistent increase in plasma PlGF levels following cancer resection. *Surg Endosc.* (2011) 25:2153–8. doi: 10.1007/s00464-010-1514-z
18. Shantha Kumara HM, Tohme ST, Herath SA, Yan X, Senagore AJ, Nasar A, et al. Plasma soluble vascular adhesion molecule-1 levels are persistently elevated during the first month after colorectal cancer resection. *Surg Endosc.* (2012) 26:1759–64. doi: 10.1007/s00464-011-2112-4
19. Shantha Kumara HM, Myers EA, Herath SA, Jang JH, Njoh L, Yan X, et al. Plasma monocyte chemotactic protein-1 remains elevated after minimally invasive colorectal cancer resection. *World J Gastrointest Oncol.* (2014) 6:413–9. doi: 10.4251/wjgo.v6.i10.413
20. Shantha Kumara HM, Gaita D, Miyagaki H, Yan X, Hearth SA, Njoh L, et al. Plasma chitinase 3-like 1 is persistently elevated during first month after minimally invasive colorectal cancer resection. *World J Gastrointest Oncol.* (2016) 8:607–14. doi: 10.4251/wjgo.v8.i8.607
21. Shantha Kumara HMC, Sutton E, Bellini GA, Yan X, Cekic V, Gandhi ND, et al. Plasma interleukin-8 levels are persistently elevated for 1 month after minimally invasive colorectal resection for colorectal cancer. *Mol Clin Oncol.* (2018) 8:471–6. doi: 10.3892/mco.2017.1538
22. Shantha Kumara HM, Gaita DJ, Miyagaki H, Yan X, Herath SA, Cekic V, et al. Minimally invasive colorectal resection is associated with significantly elevated levels of plasma matrix metalloproteinase 3 (MMP-3) during the first month after surgery which may promote the growth of residual metastases. *Surg Endosc.* (2014) 28:3322–8. doi: 10.1007/s00464-014-3612-9
23. Shantha Kumara HM, Kirchoff D, Herath SA, Jang JH, Yan X, Grieco M, et al. Plasma levels of angiopoietin-like protein 4 (ANGPTL4) are significantly lower preoperatively in colorectal cancer patients than in cancer-free patients and are further decreased during the first month after minimally invasive colorectal resection. *Surg Endosc.* (2012) 26:2751–7. doi: 10.1007/s00464-012-2269-5
24. Shantha Kumara HMC, Pettke E, Shah A, Yan X, Cekic V, Downing MA, et al. Plasma levels of the proangiogenic protein CXCL16 remains elevated for 1 month after minimally invasive colorectal cancer resection. *World J Surg Oncol.* (2018) 16:132. doi: 10.1186/s12957-018-1418-2
25. Shantha Kumara H, Miyagaki H, Herath SA, Pettke E, Yan X, Cekic V, et al. Plasma MMP-2 and MMP-7 levels are elevated first month after surgery and may promote growth of residual metastases. *World J Gastrointest Oncol.* (2021) 13:879–92. doi: 10.4251/wjgo.v13.i8.879
26. Shantha Kumara HM, Kirchoff D, Naffouje S, Grieco M, Herath SA, Dujovny N, et al. Plasma from the second and third weeks after open colorectal resection for cancer stimulates *in vitro* endothelial cell growth, migration, and invasion. *Surg Endosc.* (2012) 26:790–5. doi: 10.1007/s00464-011-1953-1
27. Shantha Kumara H, Yan XH, Pettke E, Cekic V, Gandhi ND, Bellini GA, et al. Plasma and wound fluid levels of eight proangiogenic proteins are elevated after colorectal resection. *World J Gastrointest Oncol.* (2019) 11:470–88. doi: 10.4251/wjgo.v11.i6.470
28. Finch PW, Rubin JS. Keratinocyte growth factor/fibroblast growth factor 7, a homeostatic factor with therapeutic potential for epithelial protection and repair. *Adv Cancer Res.* (2004) 91:69–136. doi: 10.1016/S0065-230X(04)91003-2
29. Miki T, Bottaro DP, Fleming TP, Smith CL, Burgess WH, Chan AM, et al. A Determination of ligand-binding specificity by alternative splicing: two distinct growth factor receptors encoded by a single gene. *Proc Natl Acad Sci USA.* (1992) 89:246–50. doi: 10.1073/pnas.89.1.246
30. Brauchle M, Angermeyer K, Hübner G, Werner S. Large induction of keratinocyte growth factor expression by serum growth factors and pro-inflammatory cytokines in cultured fibroblasts. *Oncogene.* (1994) 9:3199–204.
31. Chedid M, Rubin JS, Csaky KG, Aaronson SA. Regulation of keratinocyte growth factor gene expression by interleukin 1. *J Biol Chem.* (1994) 269:10753–7. doi: 10.1016/S0021-9258(17)34123-6
32. Niu J, Chang Z, Peng B, Xia Q, Lu W, Huang P, et al. Keratinocyte growth factor/fibroblast growth factor-7-regulated cell migration and invasion through activation of NF-kappaB transcription factors. *J Biol Chem.* (2007) 282:6001–11. doi: 10.1074/jbc.M606878200
33. Adamson IY, Bakowska J. Relationship of keratinocyte growth factor and hepatocyte growth factor levels in rat lung lavage fluid to epithelial cell regeneration after bleomycin. *Am J Pathol.* (1999) 155:949–54. doi: 10.1016/S0002-9440(10)65194-2
34. Ichimura T, Finch PW, Zhang G, Kan M, Stevens JL. Induction of FGF-7 after kidney damage: a possible paracrine mechanism for tubule repair. *Am J Physiol.* (1996) 271:F967–976. doi: 10.1152/ajprenal.1996.271.5.F967
35. Jimenez PA, Rampy MA. Keratinocyte growth factor-2 accelerates wound healing in incisional wounds. *J Surg Res.* (1999) 81:238–42. doi: 10.1006/jsre.1998.5501
36. Peng C, He Q, Luo C. Lack of keratinocyte growth factor retards angiogenesis in cutaneous wounds. *J Int Med Res.* (2011) 39:416–23. doi: 10.1177/147323001103900209
37. Pereira CT, Herndon DN, Rocker R, Jeschke MG. Liposomal gene transfer of keratinocyte growth factor improves wound healing by altering growth factor and collagen expression. *J Surg Res.* (2007) 139:222–8. doi: 10.1016/j.jss.2006.09.005
38. Gillis P, Savla U, Volpert OV, Jimenez B, Waters CM, Panos RJ, et al. Keratinocyte growth factor induces angiogenesis and protects endothelial barrier function. *J Cell Sc.* (1999) 112:2049–57. doi: 10.1242/jcs.112.12.2049
39. Xu HL, Xu J, Zhang SS, Zhu QY, Jin BH, ZhuGe DL, et al. Temperature-sensitive heparin-modified poloxamer hydrogel with affinity to KGF facilitate the morphologic and functional recovery of the injured rat uterus. *Drug Deliv.* (2017) 24:867–81. doi: 10.1080/10717544.2017.1333173
40. Wu J, Han W, Yang W, Liu H, Li C, Guo L, et al. Keratinocyte growth factor binding to fibroblast growth factor receptor 2-IIIb promotes epithelial ovarian cancer cell proliferation and invasion. *J Cancer Res Ther.* (2018) 14:S347–53. doi: 10.4103/0973-1482.235353
41. Zang XP, Lerner M, Brackett D, Pento JT. Influence of KGF on the progression of pancreatic cancer. *Anticancer Res.* (2009) 29:3417–20.
42. Yoshino M, Ishiwata T, Watanabe M, Matsunobu T, Komine O, Ono Y, et al. Expression and roles of keratinocyte growth factor and its receptor in esophageal cancer cells. *Int J Oncol.* (2007) 31:721–8. doi: 10.3892/ijo.31.4.721
43. Matsuda Y, Ueda J, Ishiwata T. Fibroblast growth factor receptor 2: expression, roles, and potential as a novel molecular target for colorectal cancer. *Patholog Res Int.* (2012) 2012:574768. doi: 10.1155/2012/574768
44. Zang XP, Lerner MR, Bahr SJ, Brackett DJ, Pento JT. A comparison of KGF receptor expression in various types of human cancer. *Cancer Genomics Proteomics.* (2006) 3:369–72.
45. Watanabe M, Ishiwata T, Nishigai K, Moriyama Y, Asano G. Overexpression of keratinocyte growth factor in cancer cells and enterochromaffin cells in human colorectal cancer. *Pathol Int.* (2000) 50:363–72. doi: 10.1046/j.1440-1827.2000.01054.x
46. Ishikawa A, Kudo M, Nakazawa N, Onda M, Ishiwata T, Takeshita T, et al. Expression of keratinocyte growth factor and its receptor in human endometrial cancer in cooperation with steroid hormones. *Int J Oncol.* (2008) 32:565–74. doi: 10.3892/ijo.32.3.565
47. Cho K, Ishiwata T, Uchida E, Nakazawa N, Korc M, Naito Z, et al. Enhanced expression of keratinocyte growth factor and its receptor correlates with venous invasion in pancreatic cancer. *Am J Pathol.* (2007) 170:1964–74. doi: 10.2353/ajpath.2007.060935
48. Narita K, Fujii T, Ishiwata T, Yamamoto T, Kawamoto Y, Kawahara K, et al. Keratinocyte growth factor induces vascular endothelial growth factor-A expression in colorectal cancer cells. *Int J Oncol.* (2009) 34:355–60.

49. Nakao S, Kuwano T, Ishibashi T, Kuwano M, Ono M. Synergistic effect of TNF-alpha in soluble VCAM-1-induced angiogenesis through alpha 4 integrins. *J Immunol.* (2003) 170:5704–11. doi: 10.4049/jimmunol.170.11.5704
50. Koch AE, Halloran MM, Haskell CJ, Shah MR, Polverini PJ. Angiogenesis mediated by soluble forms of E-selectin and vascular cell adhesion molecule-1. *Nature.* (1995) 376:517–9. doi: 10.1038/376517a0
51. Libreros S, Garcia-Areas R, Iragavarapu-Charyulu V. CHI3L1 plays a role in cancer through enhanced production of pro-inflammatory/pro-tumorigenic and angiogenic factors. *Immunol Res.* (2013) 57:99–105. doi: 10.1007/s12026-013-8459-y
52. Page-McCaw A, Ewald AJ, Werb Z. Matrix metalloproteinases and the regulation of tissue remodelling. *Nat Rev Mol Cell Biol.* (2007) 8:221–33. doi: 10.1038/nrm2125
53. Bergers G, Brekken R, McMahon G, Vu TH, Itoh T, Tamaki K, et al. Matrix metalloproteinase-9 triggers the angiogenic switch during carcinogenesis. *Nat Cell Biol.* (2000) 2:737–44. doi: 10.1038/35036374
54. Mott JD, Werb Z. Regulation of matrix biology by matrix metalloproteinases. *Curr Opin Cell Biol.* (2004) 16:558–64. doi: 10.1016/j.ceb.2004.07.010
55. Lee EJ, Kim SY, Hyun JW, Min SW, Kim DH, Kim HS. Glycitein inhibits glioma cell invasion through down-regulation of MMP-3 and MMP-9 gene expression. *Chem Biol Interact.* (2010) 185:18–24. doi: 10.1016/j.cbi.2010.02.037
56. Yoshie O, Imai T, Nomiyama H. Chemokines in immunity. *Adv Immunol.* (2001) 78:57–110. doi: 10.1016/S0065-2776(01)78002-9
57. Kim CH, Kunkel EJ, Boisvert J, Johnston B, Campbell JJ, Genovese MC, et al. Bonzo/CXCR6 expression defines type 1-polarized T-cell subsets with extralymphoid tissue homing potential. *J Clin Invest.* (2001) 107:595–601. doi: 10.1172/JCI11902
58. Isozaki T, Arbab AS, Haas CS, Amin MA, Arendt MD, Koch AE, et al. Evidence that CXCL16 is a potent mediator of angiogenesis and is involved in endothelial progenitor cell chemotaxis: studies in mice with K/BxN serum-induced arthritis. *Arthritis Rheum.* (2013) 65:1736–46. doi: 10.1002/art.37981
59. He M, Han T, Wang Y, Wu YH, Qin WS, Du LZ, et al. Effects of HGF and KGF gene silencing on vascular endothelial growth factor and its receptors in rat ultraviolet radiation-induced corneal neovascularization. *Int J Mol Med.* (2019) 43:1888–99. doi: 10.3892/ijmm.2019.4114
60. Huang T, Wang L, Liu D, Li P, Xiong H, Zhuang L, et al. FGF7/FGFR2 signal promotes invasion and migration in human gastric cancer through upregulation of thrombospondin-1. *Int J Oncol.* (2017) 50:1501–12. doi: 10.3892/ijo.2017.3927
61. Ishiwata T, Friess H, Büchler MW, Lopez ME, Korc M. Characterization of keratinocyte growth factor and receptor expression in human pancreatic cancer. *Am J Pathol.* (1998) 153:213–22. doi: 10.1016/S0002-9440(10)65562-9
62. Zhang Q, Wang P, Shao M, Chen SW, Xu ZF, Xu F, et al. Clinicopathological correlation of keratinocyte growth factor and matrix metalloproteinase-9 expression in human gastric cancer. *Tumori.* (2015) 101:566–71. doi: 10.5301/tj.5000367
63. Hong L, Han Y, Liu J, Fan D. Keratinocyte growth factor receptor: a therapeutic target in solid cancer. *Expert Opin Ther Targets.* (2015) 19:1411–148. doi: 10.1517/14728222.2015.1062474
64. Taniguchi F, Harada T, Sakamoto Y, Yamauchi N, Yoshida S, Iwabe T, et al. Activation of mitogen-activated protein kinase pathway by keratinocyte growth factor or fibroblast growth factor-10 promotes cell proliferation in human endometrial carcinoma cells. *J Clin Endocrinol Metab.* (2003) 88:773–80. doi: 10.1210/jc.2002-021062
65. Yin J, Sheng B, Pu A, Han B, Yang K, Wang Q, et al. Keratinocyte growth factor regulation of aryl hydrocarbon receptor activation in colorectal cancer cells. *Dig Dis Sci.* (2016) 61:444–52. doi: 10.1007/s10620-015-3908-1
66. Beer HD, Gassmann MG, Munz B, Steiling H, Engelhardt F, Bleuel K, et al. Expression and function of keratinocyte growth factor and activin in skin morphogenesis and cutaneous wound repair. *J Investig Dermatol Symp Proc.* (2000) 5:34–9. doi: 10.1046/j.1087-0024.2000.00009.x
67. Chandrasekher G, Pothula S, Maharaj G, Bazan HE. Differential effects of hepatocyte growth factor and keratinocyte growth factor on corneal epithelial cell cycle protein expression, cell survival, and growth. *Mol Vis.* (2014) 20:24–37.
68. McGarvey TW, Stearns ME. Keratinocyte growth factor and receptor mRNA expression in benign and malignant human prostate. *Exp Mol Pathol.* (1995) 63:52–62. doi: 10.1006/exmp.1995.1030
69. Tohme S, Simmons RL, Tsung A. Surgery for cancer: a trigger for metastases. *Cancer Res.* (2017) 77:1548–52. doi: 10.1158/0008-5472.CAN-16-1536
70. Horowitz M, Neeman E, Sharon E, Ben-Eliyahu S. Exploiting the critical perioperative period to improve long-term cancer outcomes. *Nat Rev Clin Oncol.* (2015) 12:213–26. doi: 10.1038/nrclinonc.2014.224
71. van der Bij GJ, Oosterling SJ, Beelen RH, Meijer S, Coffey JC, van Egmond M. The perioperative period is an underutilized window of therapeutic opportunity in patients with colorectal cancer. *Ann Surg.* (2009) 249:727–34. doi: 10.1097/SLA.0b013e3181a3ddbd
72. Kirman I, Belizon A, Balik E, Feingold D, Arnell T, Horst P, et al. Perioperative sargramostim (recombinant human GM-CSF) induces an increase in the level of soluble VEGFR1 in colon cancer patients undergoing minimally invasive surgery. *Eur J Surg Oncol.* (2007) 33:1169–76. doi: 10.1016/j.ejso.2007.03.014
73. Yan X, Gardner TR, Grieco M, Herath SA, Jang JH, Kirchoff D, et al. Perioperative polyphenon E- and siliphos-inhibited colorectal tumor growth and metastases without impairment of gastric or abdominal wound healing in mouse models. *Surg Endosc Surg Endosc.* (2012) 26:1856–64. doi: 10.1007/s00464-011-2114-2
74. Pantziarka P, Bouche G, Sullivan R, Ilbawi AM, Dare AJ, Meheus L. Perioperative therapies - Enhancing the impact of cancer surgery with repurposed drugs. *Eur J Surg Oncol.* (2017) 43:1985–8. doi: 10.1016/j.ejso.2017.08.010
75. Charafeddine L, D'Angio CT, Richards JL, Stripp BR, Finkelstein JN, Orlowski CC, et al. Hyperoxia increases keratinocyte growth factor mRNA expression in neonatal rabbit lung. *Am J Physiol.* (1999) 276:L105–113. doi: 10.1152/ajplung.1999.276.1.L105
76. Baskin LS, Sutherland RS, Thomson AA, Nguyen HT, Morgan DM, Hayward SW, et al. Growth factors in bladder wound healing. *J Urol.* (1997) 157:2388–95. doi: 10.1016/S0022-5347(01)64786-4
77. Marchese C, Chedid M, Dirsch OR, Csaky KG, Santanelli F, Latini C, et al. Modulation of keratinocyte growth factor and its receptor in reepithelializing human skin. *J Exp Med.* (1995) 182:1369–76. doi: 10.1084/jem.182.5.1369
78. Werner S, Peters KG, Longaker MT, Fuller-Pace F, Banda MJ, Williams LT. Large induction of keratinocyte growth factor expression in the dermis during wound healing. *Proc Natl Acad Sci USA.* (1992) 89:6896–900. doi: 10.1073/pnas.89.15.6896

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Oncology

MINI REVIEW
published: 03 January 2022
doi: 10.3389/fonc.2021.752737

Check for updates

Clinical Status and Future Prospects of Transanal Total Mesorectal Excision

Zichao Guo[1,2†], Xiaopin Ji[1,2†], Shaodong Wang[1,2†], Yaqi Zhang[1,2], Kun Liu[1,2], Changgang Wang[1,2], Yang Deng[1,2], Tao Zhang[1,2*], Xi Cheng[1,2*] and Ren Zhao[1,2*]

[1] Department of General Surgery, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China,
[2] Shanghai Institute of Digestive Surgery, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

OPEN ACCESS

Edited by:
Salman Yousuf Guraya, College of Medicine University of Sharjah, United Arab Emirates

Reviewed by:
Liang Kang, The Sixth Affiliated Hospital of Sun Yat-sen University, China
Matthias Biebl, Charité University Medicine Berlin, Germany

***Correspondence:**
Tao Zhang
woodyhom@yahoo.com
Xi Cheng
drchengxi@126.com
Ren Zhao
rjzhaoren@139.com

†These authors have contributed equally to this work

Specialty section:
This article was submitted to Surgical Oncology, a section of the journal Frontiers in Oncology

Received: *03 August 2021*
Accepted: *03 December 2021*
Published: *03 January 2022*

Citation:
Guo Z, Ji X, Wang S, Zhang Y, Liu K, Wang C, Deng Y, Zhang T, Cheng X and Zhao R (2022) Clinical Status and Future Prospects of Transanal Total Mesorectal Excision. Front. Oncol. 11:752737. doi: 10.3389/fonc.2021.752737

Low rectal cancer has always posed surgical challenges to gastrointestinal surgeons. Transanal total mesorectal excision (taTME) is a novel approach to radical resection for low rectal cancer. Compared with conventional laparoscopic TME (laTME), taTME is relevant to the benefits of better vision of the mesorectal plane, feasibility of operating in a narrow pelvis, and exact definition of distal resection margin, which may lead to a higher possibility of free circumferential resection margin, better quality of TME specimen, and lower conversion rate. Although there are concerns about its long-term oncological outcomes and complex learning curve, taTME is a promising alternative for rectal cancer. In this review, we discuss the application status and prospects of taTME.

Keywords: low rectal cancer, transanal total mesorectal excision (taTME), laparoscopic rectal surgery, minimally invasive surgery (MIS), colorectal cancer

INTRODUCTION

Rectal cancer is one of the most common cancers worldwide. The rectum is anatomically enfolded in a fatty tissue coverage known as the mesorectum, which lies in the pelvis following the sacrum and shapes to the anal canal (1). Colorectal cancer is one of the leading causes of mortality in America, with the incidence projected to continue to increase (2). The narrow pelvic space, which hinders ideal tumor resection, has always posed surgical challenges to the gastrointestinal surgeon. It is crucial to perform surgery through the correct mesorectal plane when treating rectal cancer (3). Since its inception and validation, total mesorectal excision (TME) and neoadjuvant chemoradiotherapy have become the standard treatments for CRC (4). In the early 1990s, laparoscopic surgery has become prevalent and has been validated in CRC, with benefits of faster recovery, better cosmetic effect, less postoperative pain, shorter hospital stay, and fewer complications (5–7).

After the first TME surgery was advocated by Bill Heald (1) in 1982, the principle of TME, the development of medical science and minimally invasive surgery (MIS), the experience of transanal endoscopic microsurgery (TEM) and transanal MIS (TAMIS), the method of transabdominal and transanal (TATA) (8, 9), and the concept of natural orifice transluminal endoscopic surgery (NOTES) inspire surgeons to explore a new operation, which is taTME. By its unique transanal approach for dissection, taTME is relevant to the benefits of accurate exposure of the mesorectal plane, direct vision of distal resection margin (DRM), and feasibility of overcoming technical difficulties in the narrow pelvis; thus, it may promise a higher possibility of free circumferential resection margin (CRM) and DRM, a better quality of TME specimen, and better functional outcomes over conventional TME, especially when treating male patients, obesity, narrow pelvis, and large tumors. In addition, the short-term prognosis after taTME is not inferior to that of the conventional TME (10, 11).

In this review, we aim to discuss the evolution, research status, controversy, and prospects of taTME.

THE EVOLUTION OF TATME

The History and Consensus of taTME

In 1982, the first TME was advocated by Bill Heald, which was labeled as a milestone in the history of rectal cancer surgery (1). In 2007, Whiteford et al. (3) first successfully performed TEM for rectal resection on newly thawed cadavers, which was a surgical technique of transanal local resection for early rectal cancer, using an endoscopic technique to avoid transabdominal major resections, stoma creation, and potential complications in patients with pT1N0 rectal cancer after accurate diagnosis and staging. TEM has become a hot topic in the field of surgical treatment for rectal cancer (12). TAMIS is a method of inserting a single-incision laparoscopic port into the anus and using conventional laparoscopic instruments for operation (13). The specimens resected by TEM or TAMIS can be dragged out directly through the anus, rather than through another abdominal incision, thus preventing surgical complications such as incision infection, hernia, and tumor cell implantation (13), which coincides with the concept of NOTES. The development of TATA (8, 9) makes low rectal resection and anastomosis possible. However, this method only solves the problem of anastomosis. The exposure of the low rectum and the quality of specimens, especially the quality of DRM, have not been improved (14). Advances in medical science have facilitated the development of the MIS. The principle of TME, the development of MIS, TEM, and TAMIS, the limitations of TATA, and the concept of NOTES inspired surgeons to explore a new operation, namely, taTME. In 2013, on the basis of laparoscopic-assisted taTME (LA-taTME), Dr. Zhang Hao et al. (15) from China and Leroy et al. (16) from France reported two cases of rectal resection using a complete transanal approach one after another. In the same year, Professor Heald (17) published a review called "A new solution to same old problems: transanal TME", affirming the prospects of taTME.

There is no internationally recognized definition of taTME. It is suggested that taTME should be defined as a bottom-up transanal rectal resection surgery using a TEM or TAMIS platform, following the principle of TME (18). It is recommended to abbreviate this surgery to taTME, in which "TME" is basic operation and "ta" is the modifier word to describe the transanal approach. Without special instructions, taTME usually refers to LA-taTME. When assisted by a robotic system instead of laparoscopy, the operation is called robot-assisted taTME (RA-taTME). NOTES-taTME was used to describe the operation using a complete transanal approach.

The proclaimed standard procedures for LA-taTME normally begin with transabdominal laparoscopic dissection. It can also be operated transanally, first or simultaneously, from above and below with two surgical teams.

With a customized metal sleeve for rectoscopy and corresponding equipment, the significant advantage of the TEM platform is its stability (3, 12). However, it restricts the transformation of surgical fields and the utilization of conventional laparoscopic instruments. The TAMIS platform is more prevalent in taTME based on single-incision laparoscopic surgery (19, 20). It does not require customized equipment and can utilize the single-incision laparoscopic surgery port and conventional instruments for operation (**Figure 1**).

The Learning Curve, Indications, and Contradictions of taTME

In terms of the complex learning curve of taTME, it is recommended by consensus and guidelines (18, 21–24) that this operation should be performed by certified surgeons with adequate experience of colorectal laparoscopic surgeries in large-

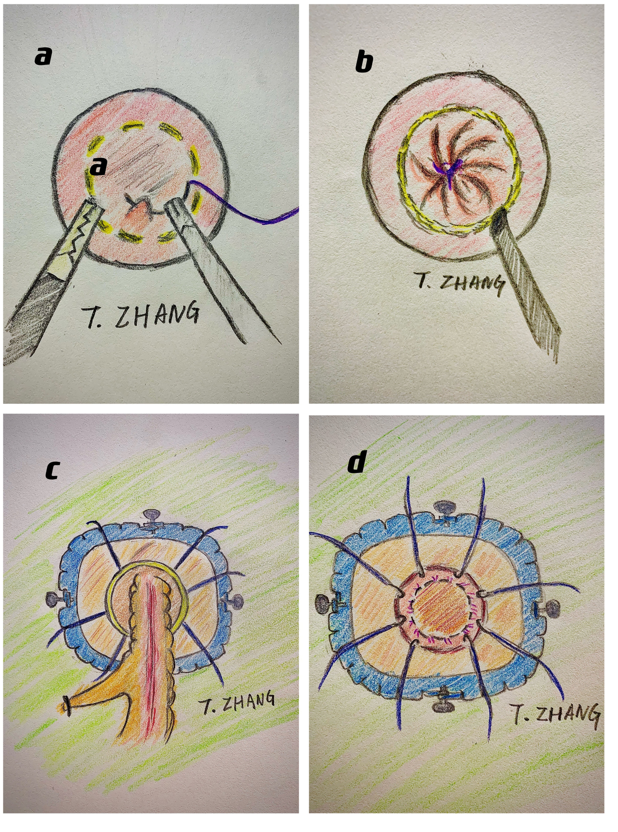


FIGURE 1 | The surgical procedures of taTME: **(A)** do purse-string suture at pre-marked distal margin; **(B)** dissect along the planned cutting line; **(C)** meet with the abdominal anatomy and drag out the specimen through anus; **(D)** anastomosis with either stapler or stitches.

volume colorectal centers. The experience of managing 30 to 60 cases has been reported to be adequate for introduction. Surgeons can achieve stable outcomes after a minimum of 50 cases are performed as primary operators. During this period, structured training programs and refined taTME protocols were essential (25).

After comprehensive considerations, indications and contradictions of taTME have been established and are constantly being refined by experts worldwide (18, 22, 23). For rectal cancer, taTME can be considered as a priority when dealing with male patients, obesity, narrow or deep pelvis, prostatic or mesorectum hypertrophy, low and anterior tumor, and tumor size >4 cm. For benign rectal diseases, taTME may be a better option when dealing with large tumors, inflammatory bowel diseases, radiation proctitis, familial adenomatous polyposis, rectal strictures, or complex fistulae.

Contradictions include obstructive rectal tumors, T4 tumors, and a history of anal strictures or injuries. In addition, taTME is not recommended when the tumor is above the peritoneal reflection.

THE RESEARCH STATUS OF TATME

The Short-Term Outcomes of taTME

As an innovative surgical approach, the short-term prognosis of taTME has attracted attention. Roodbeen et al. (26) found that after accurate staging, case recruitment, and discharge, the 2-year local recurrence (LR) rate after taTME was 3% (95% CI =2–5), which was acceptable. Yao et al. (27) included 1,283 taTME cases registered in the Chinese taTME Registry Collaborative (CTRC) from May 2010 to November 2019 for analysis. The results showed that 81.9% of specimens were complete and the rate of positive CRM was 2.8%, while the abdominal and perineal conversion rates were 0.5% and 1.9%, respectively. The 2018 CTRC annual report (19), which conducted retrospective and prospective analyses of 601 taTME cases, indicated that taTME was associated with an integral specimen and the probability of free CRM and DRM. The reports conducted by Lacy et al. (28) and Penna et al. (29), based on the International taTME Registry, including 186 and 720 cases, respectively, showed similarly acceptable short-term outcomes and good specimen quality after taTME. These findings indicated that the oncological short-term outcomes after taTME were acceptable and that taTME may be a promising alternative for rectal cancer.

The comparison between taTME and laTME has also raised concerns. Detering et al. (30), based on Dutch ColoRectal Audit, found that the rates of positive CRM were similar between the taTME and laTME groups (4.3% vs. 4.0%, p = 1.000), and the conversion rate in the taTME group was significantly lower than that in the laTME group (1.5% vs. 8.6%, p < 0.001). A meta-analysis by Lin et al. (31), including 899 cases from 12 retrospective case–control studies, found no significant difference in oncological outcomes between the taTME and laTME groups, including positive CRM, positive DRM, quality of specimen, temporary stoma, or LR. Similar results were reported by Rubinkiewicz et al. (32). In addition, the study by Zeng et al. (33), based on a randomized controlled trial (RCT), showed that positive DRM was detected in two cases in the laTME group (1.5%), while none was reported in the taTME group (p = 0.498), and the length between the tumor and DRM in the taTME group (1.4 ± 1.1) may tend to be longer than that in the laTME group (1.3 ± 0.9, p = 0.745). These findings indicate that compared with well-established laTME (5–7, 14), taTME yields non-inferior oncological short-term outcomes, considering its implementation phase. Although there is still a lack of literature, further exploration may validate the superiority of taTME in oncological regional control and long-term outcomes.

The comparison between taTME and robotic-TME is another concern. Lee et al. (34) conducted a case-matched comparison of 730 rectal cancer patients who received taTME or robotic-TME in five high-volume referral centers from 2011 to 2017. The results showed that there was no significant difference in the quality of TME specimens and the rates of positive CRM (5.6% vs. 6.0%, p = 0.839). However, the rate of positive DRM may be higher after taTME (1.8% vs. 0.3%, p = 0.051). This could be related to the steep learning curve of taTME and more caution should be paid to the exact determination of DRM, although the difference was not statistically significant. Compared with robotic-TME, the current literature suggests that taTME has non-inferior oncological short-term outcomes.

The Preoperative Assessment and Postoperative Complications of taTME

The 2015 (35) and 2019 Chinese consensus (18), as well as the Canadian taTME expert collaborative statement (23), have detailed descriptions of the indications and contraindications of taTME, but new findings may provide a new dimension. Roodbeen et al. (36) conducted an analysis of 2,653 taTME cases based on the International taTME Registry from July 2014 to January 2018, among which there were 107 cases of positive CRM (4.0%). Univariate and multivariate analyses showed that there were five factors closely related to positive CRM after taTME: tumors within 1 cm from the anus, anterior tumors, cT4 tumors, extramural venous invasion (EMVI), and involved CRM reported by preoperative baseline MRI. Another multivariate analysis by Penna (37) showed that the independent risk factors of anastomotic failure were male sex, obesity, smoking, diabetes mellitus, tumors >25 mm, excessive intraoperative blood loss, manual anastomosis, and prolonged perineal operation time. In addition, the 2018 CTRC also conducted an analysis of the risk factors of postoperative complications after LA-taTME (38). A total of 857 patients were recruited, and 563 cases were included and analyzed. Univariate and multivariate analyses showed that the independent risk factors of anastomotic leakage after LA-taTME were anastomosis without a stapler (p = 0.004), not creating a prophylactic stoma (p = 0.009), and probably tight spleen flexure (p = 0.103). These findings may be of significance for preoperative assessment and perioperative clinical decision-making of taTME and of help to reduce the incidence of positive CRM and anastomotic complications (**Tables 1–3**).

TABLE 1 | Multivariate analysis of postoperative anastomotic leakage of 563 cases after LA-taTME.

Variants	Regression Coefficient	OR (95% CI)	*p*-value
Anastomosis by stapler	−1.08	0.340 (0.163–0.708)	0.004
Prophylactic stoma	−0.932	0.394 (0.195–0.794)	0.009
Loose spleen flexure	−1.016	0.362 (0.107–1.228)	0.103

The main postoperative complication of rectal cancer is anastomosis failure. Detering et al. (30) found that the difference in anastomotic leakage rate between the taTME and laTME groups was not statistically significant (16.5% vs. 12.2%, $p = 0.116$). A meta-analysis by Lin (31) or Rubinkiewicz (32) also showed that the overall intraoperative and postoperative complications after laTME or taTME were similar, and there was no significant difference in blood loss, conversion rate, operative time, anastomotic leakage, bowel obstruction, or urinary morbidity. Using the transanal approach, the exact definition of resection margin, protecting ureter, nerve vascular bundles, and pelvic plexus, and preserving sphincters are easier to achieve under direct vision and accurate exposure. Therefore, they may promise non-inferior outcomes of complications.

The Application Status of Robotic-Assisted taTME

Robotic-assisted colorectal surgery has caused a considerable upsurge since the successful introduction of robotic systems in surgical fields. The advantages of robotic systems, including 3D vision, flexible movement, and reduction of tremor transmission, promise a better instrument maneuverability and stability in a narrow surgical field for fine anatomy (39). A robotic system is usually utilized for the transabdominal part in the implementation phase of the RA-taTME (40, 41). It may help to pass the steep learning curve and cut down the expenditures and personnel costs while simultaneously operating transabdominally and transanally, which require two surgical teams. A robotic system that was utilized for the transanal part has also been reported (40, 42–44), replacing the TEM or TAMIS platform. The advantages of robotic systems are reported to be helpful in overcoming the technical difficulties of low rectal resection and anastomosis, thus achieving good regional control.

Although there have been few small-scale studies on the application of robotic systems in taTME, the results are inspiring, in terms of the quality of TME specimens, the number of harvested lymph nodes, and the conversion rate (40–44). Further exploration of the RA-taTME and customized robotic systems is expected.

TABLE 2 | Postoperative complications of 563 cases after LA-taTME.

Complications	Number of Cases (%)
Total Postoperative Complications	115 (20.4%)
Anastomosis leakage	43 (7.6%)
Level A (do not need specific treatment)	11 (2.0%)
Level B (need non-surgical treatment)	14 (2.5%)
Level C (need surgical intervention)	14 (2.5%)
Not graded	4 (0.7%)
Postoperative bowel obstruction	14 (2.5%)
Uroschesis	8 (1.4%)
Postoperative bleeding	7 (1.2%)

TABLE 3 | Univariate analysis of postoperative anastomotic leakage of 563 cases after LA-taTME.

Variants	Number of Cases	Number of Cases of Anastomosis Leakage (Total 43 cases)	x^2 value	*p*-value
Anastomosis by stapler			3.128	0.077
Yes	440	29 (6.6%)		
No	123	14 (11.4%)		
Prophylactic stoma*			7.139	0.008
Yes	309	16 (5.2%)		
No	237	27 (11.4%)		
Loose spleen flexure*			3.232	0.072
Yes	97	3 (3.1%)		
No	454	38 (8.4%)		

**Partial data is missing.*

The Controversy of taTME

Much attention has been paid to the short-term prognosis and oncological and pathological outcomes of taTME. However, there are few reports from large-volume rectal cancer centers that focus on mid- and long-term prognosis and oncological outcomes of taTME. There is still a lack of high-level data from RCTs to support taTME. Roodbeen et al. (26) conducted a multicenter cohort study in six tertiary referral centers. The results showed that among 767 cases eligible for analysis, 24 cases had local recurrence after a median follow-up of 25.5 months, with an actuarial cumulative 2-year LR rate of 3% (95% CI = 2–5). An acceptable oncological regional control after taTME shows non-inferiority compared with the conventional TME. However, the opposite outcome of the first nationwide study from Norway raised the main controversy regarding taTME. Wasmuth et al. (45) reported 12 cases of LR (7.6%) in a total of 157 cases after taTME was performed in Norway from October 2014 to October 2018, eight of which manifested as multifocal or extensive growth. The LR rate after taTME was significantly higher than that after conventional TME (3.4%), with a short recurrence time (average, 11 months). The recurrence is characterized by rapid and multifocal growth in the pelvic cavity and lateral wall, which is different from typical manifestations. This may be related to the steep learning curve of taTME and differences in patients' general status between the taTME group and routine surgery group, such as sex, BMI, tumor size, and proportion of patients receiving neoadjuvant chemoradiotherapy. Norwegian health authorities announced a moratorium on the application of taTME.

Nonetheless, another study from the Netherlands may be explanatory and enlightening. Oostendorp et al. (46) included the first 10 taTME cases in 12 centers during their implementation phase. After a median follow-up of 21.9 months, the overall LR rate was 10%, with a mean (S.D.) recurrence time of 15.2 months. Among them, eight presented with multifocal growth. However, the overall LR rate decreased to 5.6% in the prolonged cohort and continued to decline to 4.0% after excluding the first 10 cases from each center. These findings indicate that the learning curve of taTME may be more complicated than expected. A larger sample size, a longer follow-up period, and centralization of this technique are suggested for validation in further exploration. Particular emphasis should be placed on quality control, surveillance, and refined taTME protocols. Previous experiences of MIS and transanal surgery and formatted instructions for taTME are critical factors that make a difference (25, 47). Although there is currently a lack of high-level evidence, the latest meta-analysis (48, 49) still stands for the noninferiority of taTME.

Argument also increased the quality of life and functional outcomes of patients after taTME. A meta-analysis by Heijden et al. (50) showed that there was no significant difference in the probability of patients undergoing low anterior resection syndrome (LARS) after laTME or taTME (p = 0.18). Koedam et al. (51) conducted a prospective analysis of quality of life and functional outcomes after taTME. It showed a similarity at the 6-month postoperative point compared to the preoperative baseline, except that social function and anal pain remained significantly worse. Another analysis by Veltcamp Helbach et al. (52) comparing functional outcomes between the taTME group and laTME group showed that LARS scores seemed to be higher in the taTME group at 6 months post-stoma closure, although not statistically significant. In addition, these two groups presented similar outcomes in other fields, such as sexual function and urination. It should be pointed out that cases in the taTME group are more likely to experience a low anastomosis, which may result in higher postoperative LARS scores.

THE PROSPECTS OF TATME

Using a unique transanal approach for dissection, taTME is relevant to the benefits of direct vision of DRM, accurate exposure of the mesorectal plane, and wider operating space in the narrow pelvis, which contributes to the exact definition of the resection margin, protecting the ureter, nerve vascular bundles, and pelvis plexus, and preserving sphincters; thus, it may promise a higher possibility of free CRM and DRM, a better quality of TME specimen, and better functional outcomes than conventional TME. After taTME, the specimen can be dragged out though the anus, which coincides with the concept of NOTES and the trend in surgical techniques from MIS to non-invasive treatment. Although there is a lack of high-level evidence, current large-scale studies have indicated non-inferiorities in the oncological and functional outcomes of taTME. Generally, taTME is a novel, feasible, and promising alternative surgical approach for rectal cancer that is still under investigation.

However, there are still some difficulties with taTME. First, NOTES-taTME cannot be used to explore the abdomen and ligate the root of blood supply vessels before transanal resection. Second, the learning curve of taTME is longer and more complex, especially that of NOTES-taTME. Lastly, the systematic and formatted training programs (21, 25), standardized guidelines, and refined protocols of taTME, as well as customized instruments and surgical platforms are expected to be improved.

As for long-term oncological outcomes and quality of life of taTME, there is a lack of high-level evidence. The encouraging result from TaLaR showed a declining trend in the rate of positive resection margins after taTME. Before further achievements from the international multicenter RCT COLOR III, ETAP-GRECCAR 11, and TaLaR, the priority of taTME clinical research is to guarantee the quality of radical resection and to ensure the safety of taTME, especially under the background that COLOR III has changed its primary outcome from CRM to three-year LR.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

FUNDING

This study was supported by the Shanghai Science and Technology Commission, 18ZR1424300 (RZ); the Shanghai Hospital Development Center, SHDC2020CR1026B (RZ); the Shanghai Health Commission, 2019SY058 (RZ); the National Natural Science Foundation of China, 82002475 (XC); and the Shanghai Sailing Program, 20YF1427700 (XC).

REFERENCES

1. Heald RJ, Husband EM, Ryall RD. The Mesorectum in Rectal Cancer Surgery–The Clue to Pelvic Recurrence? *Br J Surg* (1982) 69. doi: 10.1002/bjs.1800691019
2. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. *CA: Cancer J Clin* (2021) 71. doi: 10.3322/caac.21654
3. Whiteford MH, Denk PM, Swanström LL. Feasibility of Radical Sigmoid Colectomy Performed as Natural Orifice Translumenal Endoscopic Surgery (NOTES) Using Transanal Endoscopic Microsurgery. *Surg Endosc* (2007) 21. doi: 10.1007/s00464-007-9552-x
4. Heald RJ, Moran BJ, Ryall RD, Sexton R, MacFarlane JK. Rectal Cancer: The Basingstoke Experience of Total Mesorectal Excision, 1978-1997. *Arch Surg (Chicago Ill : 1960)* (1998) 133. doi: 10.1001/archsurg.133.8.894

5. Guillou PJ, Quirke P, Thorpe H, Walker J, Jayne DG, Smith AM, et al. Short-Term Endpoints of Conventional Versus Laparoscopic-Assisted Surgery in Patients With Colorectal Cancer (MRC CLASICC Trial): Multicentre, Randomised Controlled Trial. *Lancet* (2005) 365. doi: 10.1016/S0140-6736(05)66545-2
6. Quirke P, Steele R, Monson J, Grieve R, Khanna S, Couture J, et al. Effect of the Plane of Surgery Achieved on Local Recurrence in Patients With Operable Rectal Cancer: A Prospective Study Using Data From the MRC CR07 and NCIC-CTG CO16 Randomised Clinical Trial. *Lancet (London England)* (2009) 373. doi: 10.1016/S0140-6736(09)60485-2
7. Bonjer HJ, Deijen CL, Abis GA, Cuesta MA, van der Pas MHGM, de Lange-de Klerk ESM, et al. A Randomized Trial of Laparoscopic Versus Open Surgery for Rectal Cancer. *New Engl J Med* (2015) 372. doi: 10.1056/NEJMoa1414882
8. Denost Q, Adam J-P, Pontallier A, Celerier B, Laurent C, Rullier E. Laparoscopic Total Mesorectal Excision With Coloanal Anastomosis for Rectal Cancer. *Ann Surg* (2015) 261. doi: 10.1097/SLA.0000000000000855
9. Marks J, Mizrahi B, Dalane S, Nweze I, Marks G. Laparoscopic Transanal Abdominal Transanal Resection With Sphincter Preservation for Rectal Cancer in the Distal 3 Cm of the Rectum After Neoadjuvant Therapy. *Surg Endosc* (2010) 24. doi: 10.1007/s00464-010-1028-8
10. Perdawood SK, Kroeigaard J, Eriksen M, Mortensen P. Transanal Total Mesorectal Excision: The Slagelse Experience 2013-2019. *Surg Endosc* (2021) 35. doi: 10.1007/s00464-020-07454-2
11. Chen C-C, Lai Y-L, Jiang J-K, Chu C-H, Huang I-P, Chen W-S, et al. Transanal Total Mesorectal Excision Versus Laparoscopic Surgery for Rectal Cancer Receiving Neoadjuvant Chemoradiation: A Matched Case-Control Study. *Ann Surg Oncol* (2016) 23. doi: 10.1245/s10434-015-4997-y
12. Sylla P, Rattner DW, Delgado S, Lacy AM. NOTES Transanal Rectal Cancer Resection Using Transanal Endoscopic Microsurgery and Laparoscopic Assistance. *Surg Endosc* (2010) 24. doi: 10.1007/s00464-010-0965-6
13. Wexner SD, Berho M. Transanal TAMIS Total Mesorectal Excision (TME)–a Work in Progress. *Tech Coloproctol* (2014) 18. doi: 10.1007/s10151-014-1141-0
14. Kearney DE, Coffey JC. A Randomized Trial of Laparoscopic Versus Open Surgery for Rectal Cancer. *N Engl J Med* (2015) 373. doi: 10.1056/NEJMc1505367
15. Zhang H, Zhang Y-S, Jin X-W, Li M-Z, Fan J-S, Yang Z-H. Transanal Single-Port Laparoscopic Total Mesorectal Excision in the Treatment of Rectal Cancer. *Tech Coloproctol* (2013) 17. doi: 10.1007/s10151-012-0882-x
16. Leroy J, Barry BD, Melani A, Mutter D, Marescaux J. No-Scar Transanal Total Mesorectal Excision: The Last Step to Pure NOTES for Colorectal Surgery. *JAMA Surg* (2013) 148. doi: 10.1001/jamasurg.2013.685
17. Heald RJ. A New Solution to Some Old Problems: Transanal TME. *Tech Coloproctol* (2013) 17. doi: 10.1007/s10151-013-0984-0
18. Yao HW, Zhang ZT, Zheng MH. The Chinese Expert Consensus and Clinical Practice Guidance of Transanal Total Mesorectal Excision on Rectal Cancer (2019 Version). *Chin J Pract Surg* (2019) 39:1–8. doi: 10.19538/j.cjps.issn1005-2208.2019.11.01
19. Yao HW, Chen CC, Zhang HY, Yu G, Chen YG, Ren MY. Annual Report of Chinese Transanal Total Mesorectal Excision Registry Collaborative in 2018: A Nationwide Registry Study. *Chin J Pract Surg* (2019) 39:85–91. doi: 10.19538/j.cjps.issn1005-2208.2019.01.15
20. Atallah S, Albert M, Larach S. Transanal Minimally Invasive Surgery: A Giant Leap Forward. *Surg Endosc* (2010) 24. doi: 10.1007/s00464-010-0927-z
21. Francis N, Penna M, Mackenzie H, Carter F, Hompes RInternational TaTME Educational Collaborative Group. Consensus on Structured Training Curriculum for Transanal Total Mesorectal Excision (TaTME). *Surg Endosc* (2017) 31. doi: 10.1007/s00464-017-5562-5
22. Motson RW, Whiteford MH, Hompes R, Albert M, Miles WFAExpert Group. Current Status of Trans-Anal Total Mesorectal Excision (TaTME) Following the Second International Consensus Conference. *Colorectal Dis: Off J Assoc Coloproctol Great Br Ireland* (2016) 18. doi: 10.1111/codi.13131
23. Caycedo-Marulanda A, Brown CJ, Chadi SA, Ashamalla S, Lee L, Stotland P, et al. Canadian taTME Expert Collaboration (CaTaCO) Position Statement. *Surg Endosc* (2020) 34. doi: 10.1007/s00464-020-07680-8
24. Lelong B, de Chaisemartin C, Meillat H, Cournier S, Boher JM, Genre D, et al. A Multicentre Randomised Controlled Trial to Evaluate the Efficacy, Morbidity and Functional Outcome of Endoscopic Transanal Proctectomy Versus Laparoscopic Proctectomy for Low-Lying Rectal Cancer (ETAP-GRECCAR 11 TRIAL): Rationale and Design. *BMC Cancer* (2017) 17. doi: 10.1186/s12885-017-3200-1
25. Veltcamp Helbach M, van Oostendorp SE, Koedam TWA, Knol JJ, Stockmann HBAC, Oosterling SJ, et al. Structured Training Pathway and Proctoring; Multicenter Results of the Implementation of Transanal Total Mesorectal Excision (TaTME) in the Netherlands. *Surg Endosc* (2020) 34. doi: 10.1007/s00464-019-06750-w
26. Roodbeen SX, Spinelli A, Bemelman WA, di Candido F, Cardepont M, Denost Q, et al. Local Recurrence After Transanal Total Mesorectal Excision for Rectal Cancer: A Multicenter Cohort Study. *Ann Surg* (2021) 274. doi: 10.1097/SLA.0000000000003757
27. Yao H, An Y, Zhang H, Ren M, Chen C-C, Xu Q, et al. Transanal Total Mesorectal Excision: Short-Term Outcomes of 1283 Cases From a Nationwide Registry in China. *Dis Colon Rectal* (2021) 64. doi: 10.1097/DCR.0000000000001820
28. de Lacy FB, van Laarhoven JJEM, Pena R, Arroyave MC, Bravo R, Cuatrecasas M, et al. Transanal Total Mesorectal Excision: Pathological Results of 186 Patients With Mid and Low Rectal Cancer. *Surg Endosc* (2018) 32. doi: 10.1007/s00464-017-5944-8
29. Penna M, Hompes R, Arnold S, Wynn G, Austin R, Warusavitarne J, et al. Transanal Total Mesorectal Excision: International Registry Results of the First 720 Cases. *Ann Surg* (2017) 266. doi: 10.1097/SLA.0000000000001948
30. Detering R, Roodbeen SX, van Oostendorp SE, Dekker J-WT, Sietses C, Bemelman WA, et al. Three-Year Nationwide Experience With Transanal Total Mesorectal Excision for Rectal Cancer in the Netherlands: A Propensity Score-Matched Comparison With Conventional Laparoscopic Total Mesorectal Excision. *J Am Coll Surg* (2019) 228. doi: 10.1016/j.jamcollsurg.2018.12.016
31. Lin D, Yu Z, Chen W, Hu J, Huang X, He Z, et al. Transanal Versus Laparoscopic Total Mesorectal Excision for Mid and Low Rectal Cancer: A Meta-Analysis of Short-Term Outcomes. *Wideochir Inne Tech Malo Inwazyjne = Videosurg Other Miniinvasive Tech* (2019) 14. doi: 10.5114/wiitm.2019.82798
32. Rubinkiewicz M, Czerwińska A, Zarzycki P, Małczak P, Nowakowski M, Major P, et al. Comparison of Short-Term Clinical and Pathological Outcomes After Transanal Versus Laparoscopic Total Mesorectal Excision for Low Anterior Rectal Resection Due to Rectal Cancer: A Systematic Review With Meta-Analysis. *J Clin Med* (2018) 7. doi: 10.3390/jcm7110448
33. Zeng Z, Luo S, Chen J, Cai Y, Zhang X, Kang L. Comparison of Pathological Outcomes After Transanal Versus Laparoscopic Total Mesorectal Excision: A Prospective Study Using Data From Randomized Control Trial. *Surg Endosc* (2020) 34. doi: 10.1007/s00464-019-07167-1
34. Lee L, de Lacy B, Gomez Ruiz M, Liberman AS, Albert MR, Monson JRT, et al. A Multicenter Matched Comparison of Transanal and Robotic Total Mesorectal Excision for Mid and Low-Rectal Adenocarcinoma. *Ann Surg* (2019) 270. doi: 10.1097/SLA.0000000000002862
35. Ye YJ, Shen ZL, Zheng MH, Wang JP. Consensus on Transanal Total Mesorectal Excision(taTME) for Rectal Cancer. *Chin J Gastrointest Surg* (2015) 18:411–2. doi: 10.3760/cma.j.issn.1671-0274.2015.05.001
36. Roodbeen SX, de Lacy FB, van Dieren S, Penna M, Ris F, Moran B, et al. Predictive Factors and Risk Model for Positive Circumferential Resection Margin Rate After Transanal Total Mesorectal Excision in 2653 Patients With Rectal Cancer. *Ann Surg* (2019) 270. doi: 10.1097/SLA.0000000000003516
37. Penna M, Hompes R, Arnold S, Wynn G, Austin R, Warusavitarne J, et al. Incidence and Risk Factors for Anastomotic Failure in 1594 Patients Treated by Transanal Total Mesorectal Excision: Results From the International TaTME Registry. *Ann Surg* (2019) 269. doi: 10.1097/SLA.0000000000002653
38. Yao HW, Chen CC, Yu G, Ren MY, Zhang HY, Xu Q. Analysis of Complications and Risk Factors for Anastomotic Leakage After Laparoscopic-Assisted Total Rectal Mesenterectomy: A National Registry Datebase Study. *Chin J Gastrointest Surg* (2019) 3:79–84. doi: 10.3760/cma.j.issn.1671-0274.2019.03.016
39. Vignali A, Elmore U, Milone M, Rosati R. Transanal Total Mesorectal Excision (TaTME): Current Status and Future Perspectives. *Updates Surg* (2019) 71. doi: 10.1007/s13304-019-00630-7
40. Kuo L-J, Ngu JC-Y, Tong Y-S, Chen C-C. Combined Robotic Transanal Total Mesorectal Excision (R-taTME) and Single-Site Plus One-Port (R-SSPO) Technique for Ultra-Low Rectal Surgery-Initial Experience With a New Operation Approach. *Int J Colorectal Dis* (2017) 32. doi: 10.1007/s00384-016-2686-3

41. Hompes R, Rauh SM, Ris F, Tuynman JB, Mortensen NJ. Robotic Transanal Minimally Invasive Surgery for Local Excision of Rectal Neoplasms. *Br J Surg* (2014) 101. doi: 10.1002/bjs.9454
42. Verheijen PM, Consten ECJ, Broeders IAMJ. Robotic Transanal Total Mesorectal Excision for Rectal Cancer: Experience With a First Case. *Int J Med Robot + Comput Assist Surg: MRCAS* (2014) 10. doi: 10.1002/rcs.1594
43. Atallah S, Martin-Perez B, Pinan J, Quinteros F, Schoonyoung H, Albert M, et al. Robotic Transanal Total Mesorectal Excision: A Pilot Study. *Tech Coloproctol* (2014) 18. doi: 10.1007/s10151-014-1181-5
44. Gómez Ruiz M, Parra IM, Palazuelos CM, Martín JA, Fernández CC, Diego JC, et al. Robotic-Assisted Laparoscopic Transanal Total Mesorectal Excision for Rectal Cancer: A Prospective Pilot Study. *Dis Colon Rectal* (2015) 58. doi: 10.1097/DCR.0000000000000265
45. Wasmuth HH, Færden AE, Myklebust TÅ, Pfeffer F, Norderval S, Riis R, et al. Transanal Total Mesorectal Excision for Rectal Cancer Has Been Suspended in Norway. *Br J Surg* (2019) 107. doi: 10.1002/bjs.11459
46. Oostendorp SE, Belgers HJ, Bootsma BT, Hol JC, Belt EJTH, Bleeker W, et al. Locoregional Recurrences After Transanal Total Mesorectal Excision of Rectal Cancer During Implementation. *Br J Surg* (2020) 107. doi: 10.1002/bjs.11525
47. Simo V, Tejedor P, Jimenez LM, Hernan C, Zorilla J, Arrredondo J, et al. Oncological Safety of Transanal Total Mesorectal Excision (TaTME) for Rectal Cancer: Mid-Term Results of a Prospective Multicentre Study. *Surg Endosc* (2021) 35:1808–19. doi: 10.1007/s00464-020-07579-4
48. Alimova I, Chernyshov S, Nagudov M, Rybakov E. Comparison of Oncological and Functional Outcomes and Quality of Life After Transanal or Laparoscopic Total Mesorectal Excision for Rectal Cancer: A Systematic Review and Meta-Analysis. *Tech Coloproctol* (2021) 25. doi: 10.1007/s10151-021-02420-z
49. Aubert M, Mege D, Panis Y. Total Mesorectal Excision for Low and Middle Rectal Cancer: Laparoscopic Versus Transanal Approach-A Meta-Analysis. *Surg Endosc* (2020) 34. doi: 10.1007/s00464-019-07160-8
50. van der Heijden JAG, Koëter T, Smits LJH, Sietses C, Tuynman JB, Maaskant-Braat AJG, et al. Functional Complaints and Quality of Life After Transanal Total Mesorectal Excision: A Meta-Analysis. *Br J Surg* (2020) 107. doi: 10.1002/bjs.11566
51. Koedam TWA, van Ramshorst GH, Deijen CL, Elfrink AKE, Meijerink WJHJ, Bonjer HJ, et al. Transanal Total Mesorectal Excision (TaTME) for Rectal Cancer: Effects on Patient-Reported Quality of Life and Functional Outcome. *Tech Coloproctol* (2017) 21. doi: 10.1007/s10151-016-1570-z
52. Veltcamp Helbach M, Koedam TWA, Knol JJ, Velthuis S, Bonjer HJ, Tuynman JB, et al. Quality of Life After Rectal Cancer Surgery: Differences Between Laparoscopic and Transanal Total Mesorectal Excision. *Surg Endosc* (2019) 33. doi: 10.1007/s00464-018-6276-z

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Oncology

ORIGINAL RESEARCH
published: 12 January 2022
doi: 10.3389/fonc.2021.768299

Comparative Effectiveness of Enhanced Recovery After Surgery Program Combined With Single-Incision Laparoscopic Surgery in Colorectal Cancer Surgery: A Retrospective Analysis

Changgang Wang[1†], Haoran Feng[1†], Xiaoning Zhu[2†], Zijia Song[1], You Li[1], Yiqing Shi[1], Yimei Jiang[1], Xianze Chen[1], Tao Zhang[1], Ren Zhao[1*] and Kun Liu[1*]*

[1] Department of General Surgery, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China,
[2] Department of Neurology Department, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China

Edited by:
Cheng-Le Zhuang, Tongji University, China

Reviewed by:
Bo Lv, Huazhong University of Science and Technology, China
Yifeng Yu, First Affiliated Hospital of Xiamen University, China

***Correspondence:**
Ren Zhao
zhaorensurgeon@aliyun.com
Kun Liu
lookiere@126.com
Tao Zhang
woodyhom@yahoo.com

[†]These authors have contributed equally to this work

Specialty section:
This article was submitted to Surgical Oncology, a section of the journal Frontiers in Oncology

Received: *31 August 2021*
Accepted: *20 December 2021*
Published: *12 January 2022*

Citation:
Wang C, Feng H, Zhu X, Song Z, Li Y, Shi Y, Jiang Y, Chen X, Zhang T, Zhao R and Liu K (2022) Comparative Effectiveness of Enhanced Recovery After Surgery Program Combined With Single-Incision Laparoscopic Surgery in Colorectal Cancer Surgery: A Retrospective Analysis. Front. Oncol. 11:768299. doi: 10.3389/fonc.2021.768299

Background: Recently, enhanced recovery after surgery (ERAS) has been widely used in the perioperative management of colorectal cancer (CRC). This study aimed to evaluate the safety and feasibility of ERAS combined with single-incision laparoscopic surgery (SILS) in CRC surgery.

Methods: This was a retrospective study of patients with CRC who underwent surgery between April 2018 and April 2020 in Ruijin Hospital(North), Shanghai Jiaotong University School of Medicine. The patients were divided into three groups: group A (n=138), patients who underwent traditional multiport laparoscopic colectomy with conventional perioperative management; group B (n=63), patients who underwent SILS; and group C (n=51), patients who underwent SILS with ERAS.

Results: Overall, 252 participants were included in the retrospective study. The median operation time (min) in group B and group C was shorter than that in group A (group A 134.0 ± 42.5; group B 117 ± 38.9; group C 111.7 ± 35.4, p=0.004). The estimated surgical blood loss (ml) was lower in groups B and C than in group A (group A 165.1 ± 142.2; group B 122.0 ± 79.4; group C 105.2 ± 55.8, p=0.011). The length of surgical incision (cm) was shorter in groups B and C than in group A (group A 7.34 ± 1.05; group B 5.60 ± 0.80; group C 5.28 ± 0.52, p<0.001). The time before first flatus (hours) in group C was shorter than in groups A and B (group A 61.85 ± 21.14; group B 58.30 ± 20.08; group C 42.06 ± 23.72; p<0.001). The days prior to the administration of free oral fluids in group C was shorter than in groups A and B (group A 4.79 ± 1.28; group B 4.67 ± 1.11; group C 2.62 ± 0.64; p<0.001). The days of prior solid diet was less in group C than ingroups A and B (group A 7.22 ± 3.87; group B 7.08 ± 3.18; group C 5.75 ± 1.70; p=0.027). The postoperative length of stay (LOS) was less in group C compared with that in groups A and B (group A 9.46 ± 4.84 days; group B 9.52 ± 7.45 days; group C 7.20 ± 2.37 days; p=0.023). The visual analog scale (VAS) scores on day 0, 1, and 2 in groups B and C were lower than those in group A (day 0, p<0.001; day 1, p<0.001; day 2, p=0.002), while the VAS score on day 3 showed no differences in the three groups (group A 1.29 ± 1.38; group B 0.98 ± 1.24; group C 0.75 ± 0.64, p=0.018).

Conclusion: The findings suggest that SILS combined with ERAS may be a feasible and safe procedure for CRC surgery because it provides favorable cosmetic results, early dietary resumption, shorter hospital stays, and appropriate control of postoperative pain without increases in complications or readmission rates compared to conventional perioperative care with SILS or conventional laparoscopic surgery(CLS) of CRC. Further prospective randomized controlled studies are needed to enhance evidence-based medical evidence.

Keywords: ERAS, SILS, colorectal cancer, retrospective analysis, CLS

INTRODUCTION

According to global cancer statistics, colorectal cancer (CRC) is the third most common cancer worldwide and the second leading cause of mortality (1).With the rapid development of laparoscopic technology and instruments, laparoscopic radical resection of CRC has been proven safe and effective in multiple randomized controlled trials compared with traditional open surgery (2–5). Moreover, laparoscopic surgery has many advantages, such as less trauma, good cosmetic effect, less postoperative pain, and shorter hospital stay (6–8).Single incision laparoscopic colorectal surgery (SILS) has been developed based on traditional laparoscopic surgery. It was first reported in 2008 that Bucher et al. (9) successfully performed a single-hole laparoscopic right hemicolectomy for a patient with colonic polyps and achieved good results. Since our colorectal center performed the first single-incision laparoscopic radical resection of CRC in 2013, more than 400 single-incision laparoscopic radical resections of CRC have been performed, including right hemicolectomy, left hemicolectomy, sigmoid hemicolectomy, and high rectal surgery. Through retrospective analysis and prospective RCT research, it was confirmed that the safety and curative effects of single-incision laparoscopic radical resection of CRC are not inferior to those of traditional laparoscopic surgery (10, 11).

Since its introduction in 1997 by Professor Kehlet (12), enhanced recovery after surgery (ERAS) has achieved great success in clinical practice worldwide and has shown advantages in CRC surgery. Using such a multimodal stress-minimizing approach has been shown to reduce rates of morbidity, improve recovery, and shorten the length of stay (LOS) after a major colorectal surgery (13).

However, the effectiveness of the ERAS program combined with SILS in CRC surgery is unclear. Few clinical studies have reported the effectiveness of the ERAS program combined with SILS in CRC surgery (14). In this study, we performed a retrospective analysis to evaluate the effect of the ERAS program with SILS in CRC surgery.

METHODS

Patients

A retrospective cohort study was performed on 252 patients who underwent SILS or traditional laparoscopic surgery for CRC at the Department of Colorectal Surgery, Ruijn Hospital(North), Shanghai Jiaotong University School of Medicine from April 2018 to April 2020. All patients were divided into three groups: group A (n=138), patients who underwent traditional multiport laparoscopic colorectal surgery with conventional perioperative management; group B (n=63), patients who underwent SILS; and group C (n=51), patients who underwent SILS with the ERAS concept. The study was approved by the local research ethics committee of Ruijn Hospital(North), Shanghai Jiaotong University School of Medicine and followed the international and national regulations in accordance with the Declaration of Helsinki. A written informed consent was obtained from all patients, allowing us to store their data in our hospital database and use it for clinical research.

The inclusion criteria were as follows: (1) tumor clinical stage IA to IIIC according to the seventh edition of the American Joint Committee on Cancer (AJCC); (2) tumor diameter ≤ 5 cm; and (3) body mass index (BMI) ≤ 35 kg/m^2. The exclusion criteria were as follows: (1) metastatic disease; (2) simultaneous or metachronous multiple cancers with disease-free survival ≤ 5 years; (3) simultaneous surgery for other diseases; (4) emergency operation; (5) neoadjuvant chemoradiotherapy; and (6) ASA IV or V according to the American Society of Anesthesiologists classification (ASA). The ERAS group had other exclusion criteria: (1) cT4b; and (2) tumor diameter ≥ 4 cm.

TABLE 1 | Difference of perioperative management between ERAS group and traditional control group.

Treatment Measures	ERAS Group	Traditional Control Group
Rehabilitation education	Anaesthesiologic, cardiologic and surgical counselling	No
Preoperative bowel preparation	Unconventional,Only for rectal resection	Preoperative enema the evening before surgery
Preoperative fasting	6 h, solid foods (inedible);2 h, Clear fluids,Carbohydrates oral loading(edible)	12 h
Nasogastric tub	Unconventional,Orogastric tube placed at the beginning of surgery, removed at the end of the procedure	Unlimited
Multi-modal anaesthetic protocol	General anesthesia, ultrasound-guided transversus abdominis plane block,Injection of local anaesthetics on the region of surgical wounds	General anesthesia
Prevention of intraoperative hypothermia	Warming device,Warmed intravenous fluids	Unconvention
Urinary drainage	1-2 d	3-5 d
Abdominal drainage	Often placed 1-2 d	3-5 d
Modes of postoperative analgesia	Injection of analgesic drugs other than opioids	Venous self-control analgesic pump(o pioid pain killers used)
Perioperative nutritional care	Nutritional screening highly recommended considering BMI and albumin level	Nutritional screening highly recommended considering BMI and albumin level
Early mobilisation	Full mobilization on the first postoperative day	Unlimited
Prophylaxis against thromboembolism	Compression stockings,LMWH according to Caprini score	Unlimited
Postoperative oral feeding	Light hospital diet and oral nutritional supplements on the first postoperative day, full hospital diet in the second postoperative day	Unlimited

Perioperative Management

Groups A and B were treated with traditional perioperative management, and group C was treated with ERAS according to the protocol of the ERAS Society. The perioperative protocols of the traditional method and ERAS are shown in **Table 1**.

Surgical Procedures

Six qualified surgeons with over 50 cases of laparoscopic CRC surgery performed the operations in the conventional laparoscopic surgery (CLS) group. The SILS group operations were all performed by the same surgeon (Z.R.), who had performed over 200 cases of SILS for CRC.

After general anesthesia, the patients were placed in optimal positions according to the surgical approach. In general, straddle-type supine, Trendelenberg with left-tilted or right-tilted position was used in right colectomy or left colectomy, respectively. Additionally, modified lithotomy, Trendelenberg, right-tilted position was used in sigmoidectomy and anterior resection.

In the SILS group, a SILS™ Port (Covidien, Mansfield, MA, USA) with three 5-mm cannulas inserted or a Star-Port (Surgaid®, Guangzhou, China) consisting of three fixed instrument channels (one 5-mm, two 10-mm, and one 12-mm) was installed through a 2-3 cm midline periumbilical incision. A 30° laparoscope, a 0° flexible laparoscope (LTF-VP, Olympus Medical Systems, Tokyo, Japan), or an Olympus 3D laparoscope were used based on the choice of port. In cases using the SILS™ Port, the main operating cannula was changed from 5 mm to 12 mm when using Endo GIA™. In the CLS group, the operation was performed with 3-5 trocars, including a 12-mm trocar for a 30° laparoscope or a 3D laparoscope in the periumbilical area. The main operating trocar was 12-mm, while the remaining trocars was 5-mm. All surgeries in both groups were performed using conventional laparoscopic instruments.

All surgeries were performed according to the same oncologic principles, including complete mesocolic excision for colon cancer and total mesorectal excision for rectal cancer with D3 lymph node dissection. The medial-to-lateral or lateral-to-medial approach was adopted depending on the surgeon. For sigmoidectomy and anterior resection, mobilization of the splenic flexure was not performed routinely, except in cases of a lack of redundancy of the sigmoid colon or excessive anastomotic tension. Prophylactic ileostomy was performed depending on the anastomosis.

The specimen was retrieved through the wound protector installed through a transumbilical incision (SILS group) or a 3-4 cm additional incision (CLS group). The draining tube was extracted through the incision in the SILS group or through the main operating channel in the CLS group. The incisions were closed using an absorbable monofilament. Details of the surgical procedure were described in our previous reports (10, 11).

Outcomes

The primary outcome was early morbidity, defined as postoperative complications observed within 30 days after surgery. It was graded according to the Clavien-Dindo classification. The secondary outcomes included intraoperative outcomes (operation time, estimated blood loss, incision length, and conversion rate), postoperative pain score, postoperative recovery (time to first ambulation, flatus, liquid diet and soft diet, LOS), and pathologic outcomes (tumor size, number of harvested lymph nodes, and proximal and distal resection margins). The incision length was defined as the sum of all the incision lengths. Postoperative pain was recorded using the visual analog scale (VAS) pain score (0-10 points) on postoperative day 0, 1, 2, and 3. Pathological outcomes were evaluated by pathologists. Follow-up was consistent with the

National Comprehensive Cancer Network guidelines. Recurrence was confirmed using radiological and histological methods.

Statistical Analyses

Statistical analyses were performed using SPSS (version 22.0, SPSS Inc. Chicago, IL, USA). Continuous variables were presented as mean ± standard deviation and categorical variables were described as numbers with percentages. The one-way analysis of variance (ANOVA) test were used for continuous variables of three groups, whereas proportions were compared using Pearson chi-square($\chi 2$) test or Fisher's exact test, as appropriate. All P values were 2-tailed, statistical significance was accepted for P values of <0.05.

RESULTS

Baseline Characteristics and Types Of Surgeries

As shown in **Table 2**, there was no significant difference in terms of age, sex, BMI, preoperative serum CEA, and ASA grade among 3 groups. The types of surgeries are also shown in **Table 2**.

Intraoperative and Perioperative Outcomes

Intraoperative and postoperative outcomes are shown in **Table 3**. The mean operation time in groups B and C, who underwent SILS surgery, was shorter than that in group A, who underwent traditional laparoscopic surgery (group A 134.0 ± 42.5 min; group B 117 ± 38.9 min; group C 111.7 ± 35.4 min, p=0.004). The estimated surgical blood loss (ml) of those who underwent SILS was less in groups B and C than in group A (group A 165.1 ± 142.2; group B 122.0 ± 79.4; group C 105.2 ± 55.8, p=0.011). The length of surgery incision (cm) was also shorter in groups B and C than in group A (group A 7.34 ± 1.05; group B 5.60 ± 0.80; group C 5.28 ± 0.52, p<0.001). In contrast, blood transfusion rate (group A 15.2%; group B 14.3%; group C 9.8%, p=0.630) and intraoperative complications like vascular injury or conversion to open surgery (p=0.623) showed no difference among the three groups.

Pathologic Outcomes

The tumor size, proximal and distal resection margins, number of harvested lymph nodes, cell type, tumor differentiation, neurovascular invasion, perineural invasion, and pathologic stage were similar among the three groups (**Table 4**). No positive circumferential resection margins were found in the cases of rectal cancer.

Postoperative Function Analysis

Postoperative function analysis was performed according to the surgical procedures as shown in **Table 5**. The time before first flatus (hours) in group C, who underwent SILS and ERAS was shorter than in groups A and B, who underwent routine preoperative preparation (group A 61.85 ± 21.14; group B 58.30 ± 20.08; group C 42.06 ± 23.72, p<0.001). Furthermore, the days prior to the administration of free oral fluids in group C was shorter than in groups A and B (group A 4.79 ± 1.28; group B 4.67 ± 1.11; group C 2.62 ± 0.64, p<0.001). The days prior to the resumption of solid diet was less in groups A and B (group A 7.22 ± 3.87; group B 7.08 ± 3.18; group C 5.75 ± 1.70, p=0.027). The postoperative LOS (days) was also less in groups A and B (group A 9.46 ± 4.84; group B 9.52 ± 7.45; group C 7.20 ± 2.37, p=0.023); The VAS scores in days 0, 1, and 2 in groups B and C, who underwent SILS were lower than group A, who underwent

TABLE 2 | Patient demographics, baseline characteristics, and type of operations performed according to tumor location.

Parameter	CLS	SILS	SILS (ERAS)	*P* value
Number of patients, n	138	63	51	
Age (years)				0.052
Mean ± SD	62.12 ± 12.09	60.84 ± 11.59	57.47±10.26	
Sex, n (%)				0.697
Males	88 (63.8)	44 (69.8)	33 (64.7)	
Females	50 (36.2)	19 (30.2)	18 (35.3)	
BMI (kg/m^2)				0.596
Mean ± SD	23.40±3.07	23.40±3.07	23.40±3.07	
Preoperative serum CEA (ng/mL),n (%)				0.112
≤5	99 (71.7)	46 (73.0)	44 (86.3)	
>5	39 (28.3)	17 (27.0)	7 (13.7)	
ASA grade, n (%)				0.333
I	42 (30.4)	19 (30.2)	11 (21.6)	
II	80 (58.0)	35 (55.6)	37 (72.5)	
III	16 (11.6)	9 (14.3)	3 (5.9)	
Type of procedure, n (%)				–
Right hemicolectomy	18 (13.0)	20 (31.7)	15 (29.4)	
Left hemicolectom	15 (12.6)	5 (7.9)	3 (5.9)	
Sigmoidectomy	23 (16.7)	20 (31.7)	14 (27.5)	
Rectal resection	74 (53.6)	18 (28.6)	19 (37.3)	
Hartmann	8 (5.8)	0 (0.0)	0 (0.0)	

BMI, body mass index; ASA, American society of anesthesiologists; CEA, carcinoembryonic antigen.

TABLE 3 | Operative data.

Parameter	CLS	SILS	SILS (ERAS)	*P* value
Total surgical time, minutes				<0.001
Mean ± SD	134.01±42.50[a,b]	115.86±37.27[b]	112.49±26.68[a]	
Estimated surgical blood loss, mL				0.004
Mean ± SD	165.07±142.17[c,d]	121.27±79.22[d]	109.41±79.41[c]	
Length of surgery incision (cm)				<0.001
Mean ± SD	7.34±1.05[e,f]	5.60±0.80[f]	5.28±0.52[c]	
Blood transfusion (cases), n (%)	21 (15.2)	9 (14.3)	5 (9.8)	0.630
Intraoperative complications, n (%)				
Vascular injury	14 (10.1)	6 (9.5)	7 (13.7)	0.623
Conversion to open surgery	0 (0.0)	0 (0.0)	0 (0.0)	:

[a]*CLS vs SILS (ERAS),P=0.002;.*
[b]*CLS vs SILS,P=0.006.*
[c]*CLS vs SILS (ERAS),P=0.013;.*
[d]*CLS vs SILS,P=0.046.*
[e]*CLS vs SILS (ERAS),P<0.00.*
[f]*CLS vs SILS,P<0.001.*

TABLE 4 | Data related to tumor pathology.

Parameter	CLS	SILS	SILS (ERAS)	*P* value
Histology type, n (%)				0.116
Adenocarcinoma	122 (88.4)	52 (82.5)	39 (76.5)	
Others	16 (11.6)	11 (17.5)	12 (23.5)	
Tumor differentiation, n (%)				0.427
Well differentiated	13 (9.4)	10 (15.9)	9 (17.6)	
Moderately differentiated	117 (84.8)	51 (81.0)	39 (76.5)	
Poorly differentiated	8 (5.8)	2 (3.2)	3 (5.9)	
Tumor depth (T classification), n (%)				0.141
T1	13 (9.4)	7 (11.1)	6 (11.8)	
T2	32 (23.2)	13 (20.6)	17 (33.3)	
T3	46 (33.3)	29 (46.0)	20 (39.2)	
T4	47 (34.1)	14 (22.2)	8 (15.7)	
Lymph node metastasis, n (%)				0.382
No	93 (67.4)	41 (65.1)	39 (76.5)	
Yes	45 (32.6)	22 (34.9)	12 (23.5)	
TNM stage, n (%)				0.453
I	40 (29.0)	18 (28.6)	21 (41.2)	
II	57 (41.3)	23 (36.5)	18 (35.3)	
III	41 (29.7)	22 (34.9)	12 (23.5)	
Largest tumor diameter (cm)				0.118
Mean ± SD	3.96±1.81	3.65±1.39	3.45±1.07	
Lymph nodes in resected specimen, n				0.545
Mean ± SD	13.70±2.35	13.48±2.77	14.00±2.65	
Proximal margin (cm),Mean ± SD				
Colon	7.45±4.96	7.68±3.82	8.29±5.81	0.722
Rectum	7.79±3.48	5.91±1.73	7.22±3.71	0.107
Distal margin (cm), Mean ± SD				
Colon	6.41±3.69	7.16±5.76	7.54±5.16	0.519
Rectum	2.31±0.97	2.93±1.28	2.63±1.55	0.097
Lymphovascular invasion, n (%)				0.323
No	95 (68.8)	48 (76.2)	40 (78.4)	
Yes	43 (31.2)	15 (23.8)	11 (21.6)	
Perineural invasion, n (%)				0.635
No	93 (67.4)	43 (68.3)	38 (74.5)	
Yes	45 (32.6)	20 (31.7)	13 (25.5)	

TNM, tumor-node-metastasis.

traditional laparoscopic surgery (day 0 p<0.001; day 1 p<0.001; day 2 p=0.002), while the VAS score in day 3 showed no differences among the three groups (group A 1.29 ± 1.38; group B 0.98 ± 1.24; group C 0.75 ± 0.64, p=0.018). The 30-day mortality postoperative rate was zero in the three groups.

DISCUSSION

The ERAS program has been widely combined with laparoscopic colorectal surgery using a multimodal stress-minimizing approach to reduce perioperative stress, maintain postoperative

TABLE 5 | Data related to postoperative function.

Parameter	CLS	SILS	SILS (ERAS)	*P* value
Duration before first flatus (hours)	61.85±21.14[a]	58.30±20.08[b]	42.06±23.72[a,b]	<0.001
Days prior free oral fluids (days)	4.79±1.28[c]	4.67±1.11[d]	2.62±0.64[c,d]	<0.001
Duration prior solid diet (days)	7.22±3.87[e]	7.08±3.18	5.75±1.70[e]	0.027
Postoperative length of stay (days)	9.46±4.84[f]	9.52±7.45[g]	7.20±2.37[f,g]	0.023
VAS score				
Day 0	3.14±2.08[h]	2.43±1.48[i]	1.71±0.88[h,i]	<0.001
Day 1	3.72±1.62[j]	3.22±1.49[k]	2.24±0.97[j,k]	<0.001
Day 2	2.43±1.52[m]	1.98±1.37	1.67±0.93[m]	0.002
Day 3	1.29±1.38[n]	0.98±1.24	0.75±0.64[n]	0.018
30-day mortality, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	

VAS,Visual analogue scale.
a,c,e,f,h,j,m,n CLS vs SILS (ERAS) b,d,g,I,k SILS vs SILS (ERAS).
[a]*P<0.001;*
[b]*P<0.001;*
[c]*P<0.001;*
[d]*P<0.001;*
[e]*P=0.025;*
[f]*P=0.009;*
[g]*P=0.020;*
[h]*P<0.001;*
[i]*P=0.030;*
[j]*P<0.001;*
[k]*P<0.001;*
[m]*P=0.001;*
[n]*P=0.007.*

physiological function, accelerate recovery after surgery, reduce rates of morbidity, improve recovery, and shorten the LOS after a major colorectal surgery (15–18). SILS for CRC was first reported in 2008 and developed rapidly in recent years in both the number and type of operations and the type of operation; however, compared with CLS, the safety and radical effects showed no difference in SILS CRC, while the latter showed potential benefits of reducing postoperative pain and better cosmetic effects, which were performed by experienced surgeons (19–25). The combination of ERAS and SILS in CRC may have a synergistic effect on the recovery of patients. Min Ki Kim et al. reported that an ERAS program combined with SILS showed early dietary resumption, shorter hospital stays, and appropriate control of postoperative pain without increases in complications or readmission rates in CRC patients compared to a conventional perioperative care with laparoscopic CRC surgery (14). However, patients with rectal, descending colon, and transverse CRCs were excluded.

In this study, we found that the median operation time was shorter in the SILS and SILS + ERAS group than in the CLS group. There may be two reasons for this result. First, the patients who underwent SILS had another set of exclusion criteria: (1) cT4b; and (2) tumor diameter ≤ 4 cm. Second, all SILS were performed with a 3D laparoscope and flexible laparoscope, which was not applied in the CLS group.

The total incision length is often used in the evaluation of cosmetic effects. In this study, the SILS ± ERAS group had a shorter incision length because of fewer trocars. However, the cosmetic effect is a subjective feeling that is not only determined by the incision length. Some reported scales and questionnaires may be more suitable for evaluating cosmetic effects. The SILS ± ERAS group showed lower VAS scores on postoperative day 0, 1, and 2 with similar postoperative analgesic usage, which may be related to fewer incisions. The VAS score and cosmetic effect evaluation will affect the postoperative psychological recovery. The pathologic outcomes showed no differences among the three groups, and the radical effect was reliable in the SILS ± ERAS group.

The recovery process in the SILS+ERAS group was significantly faster compared to the SILS and CLS group, including the time before first flatus, days prior to administration of free oral fluids, days prior to resumption of solid diet, and the postoperative LOS (26).

At present, SILS and ERAS programs have rapidly developed worldwide for CRC. Although the SILS technology is mainly limited by the technical challenges, in the future, with the integration of instrument functions and the application of robotic surgery, the difficulty of SILS will be further reduced, and it will be popularized and applied more widely. Furthermore, the combination with ERAS may be a priority for the appropriate patients, which can reduce the hospitalization time and cost of hospitalization, and obtain better cosmetic effects and psychological rehabilitation.

This study had several limitations. First, this was a small retrospective study. Therefore, selection bias could not be excluded. However, this bias was minimized by selecting study subjects with the same eligibility criteria from the two different data sets. Second, all SILS were performed by the same senior surgeon, but the CLS was performed by six different surgeons, which may have led to a bias in operation time, therapy after surgery, and LOS. However, the bias was small and the same in different groups. Third, another group of CLS+ERAS cases may need to be more convincing. In fact, the number of these cases was very small, so they were not included in the statistics, but it did not affect the conclusion of the study.

CONCLUSIONS

These findings suggest that SILS combined with ERAS may be a feasible and safe procedure for CRC surgery because it provides favorable cosmetic results, early dietary resumption, shorter hospital stays, and appropriate control of postoperative pain without increases in complications or readmission rates. Further prospective randomized controlled studies are needed to enhance evidence-based medical evidence.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

CW and HF conceived of the study, and prepared the manuscript draft. TZ, KL, and RZ critically revised the manuscript for important intellectual content. XZ, ZS, YL, YS, YJ, and XC performed the data collection. All authors contributed to the article and approved the submitted version.

FUNDING

This study was supported by Advanced and Appropriate Technology Promotion Projects of Shanghai Municipal Health Commission (2019SY058), Clinical Skills and Innovations 3-year program of Shanghai Hospital Development Center (16CR2064B) and the Special Clinical Research Projects of Shanghai Municipal Health Commission (20204Y0006).

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* (2021) 71(3):209–49. doi: 10.3322/caac.21660
2. Lacy AM, Garcia-Valdecasas JC, Delgado S, Castells A, Taura P, Pique JM, et al. Laparoscopy-Assisted Colectomy Versus Open Colectomy for Treatment of non-Metastatic Colon Cancer: A Randomised Trial. *Lancet* (2002) 359(9325):2224–9. doi: 10.1016/S0140-6736(02)09290-5
3. Veldkamp R, Kuhry E, Hop WC, Jeekel J, Kazemier G, Bonjer HJ, et al. Laparoscopic Surgery Versus Open Surgery for Colon Cancer: Short-Term Outcomes of a Randomised Trial. *Lancet Oncol* (2005) 6(7):477–84. doi: 10.1016/S1470-2045(05)70221-7
4. Guillou PJ, Quirke P, Thorpe H, Walker J, Jayne DG, Smith AM, et al. Short-Term Endpoints of Conventional Versus Laparoscopic-Assisted Surgery in Patients With Colorectal Cancer (MRC CLASICC Trial): Multicentre, Randomised Controlled Trial. *Lancet* (2005) 365(9472):1718–26. doi: 10.1016/S0140-6736(05)66545-2
5. Lujan J, Valero G, Biondo S, Espin E, Parrilla P, Ortiz H. Laparoscopic Versus Open Surgery for Rectal Cancer: Results of a Prospective Multicentre Analysis of 4,970 Patients. *Surg Endosc* (2013) 27(1):295–302. doi: 10.1007/s00464-012-2444-8
6. Clinical Outcomes of Surgical Therapy Study G, Nelson H, Sargent DJ, Wieand HS, Fleshman J, Anvari M, et al. A Comparison of Laparoscopically Assisted and Open Colectomy for Colon Cancer. *N Engl J Med* (2004) 350 (20):2050–9. doi: 10.1056/NEJMoa032651
7. Kuhry E, Schwenk WF, Gaupset R, Romild U, Bonjer HJ. Long-Term Results of Laparoscopic Colorectal Cancer Resection. *Cochrane Database Syst Rev* (2008) 2):CD003432. doi: 10.1002/14651858.CD003432.pub2
8. Schwenk W, Haase O, Neudecker J, Muller JM. Short Term Benefits for Laparoscopic Colorectal Resection. *Cochrane Database Syst Rev* (2005) 3): CD003145. doi: 10.1002/14651858.CD003145.pub2
9. Bucher P, Pugin F, Morel P. Single Port Access Laparoscopic Right Hemicolectomy. *Int J Colorectal Dis* (2008) 23(10):1013–6. doi: 10.1007/s00384-008-0519-8
10. Jiang Y, Song Z, Cheng X, Liu K, Shi Y, Wang C, et al. Clinical and Oncological Outcomes of Single-Incision vs. Conventional Laparoscopic Surgery for Rectal Cancer. *Surg Endosc* (2020) 34(12):5294–303. doi: 10.1007/s00464-019-07317-5
11. Song Z, Li Y, Liu K, Jiang Y, Shi Y, Ji X, et al. Clinical and Oncologic Outcomes of Single-Incision Laparoscopic Surgery for Right Colon Cancer: A Propensity Score Matching Analysis. *Surg Endosc* (2019) 33(4):1117–23. doi: 10.1007/s00464-018-6370-2
12. Kehlet H. Multimodal Approach to Control Postoperative Pathophysiology and Rehabilitation. *Br J Anaesth* (1997) 78(5):606–17. doi: 10.1093/bja/78.5.606
13. Gustafsson UO, Scott MJ, Hubner M, Nygren J, Demartines N, Francis N, et al. Guidelines for Perioperative Care in Elective Colorectal Surgery: Enhanced Recovery After Surgery (ERAS((R))) Society Recommendations: 2018. *World J Surg* (2019) 43(3):659–95. doi: 10.1007/s00268-018-4844-y
14. Kim MK, Kim JG, Lee G, Won DD, Lee YS, Kye BH, et al. Comparison of the Effects of an ERAS Program and a Single-Port Laparoscopic Surgery on Postoperative Outcomes of Colon Cancer Patients. *Sci Rep* (2019) 9(1):11998. doi: 10.1038/s41598-019-48526-1
15. Basse L, Raskov HH, Hjort Jakobsen D, Sonne E, Billesbolle P, Hendel HW, et al. Accelerated Postoperative Recovery Programme After Colonic Resection Improves Physical Performance, Pulmonary Function and Body Composition. *Br J Surg* (2002) 89(4):446–53. doi: 10.1046/j.0007-1323.2001.02044.x
16. Borzellino G, Francis NK, Chapuis O, Krastinova E, Dyevre V, Genna M. Role of Epidural Analgesia Within an ERAS Program After Laparoscopic Colorectal Surgery: A Review and Meta-Analysis of Randomised Controlled Studies. *Surg Res Pract* (2016) 2016:7543684. doi: 10.1155/2016/7543684
17. Gustafsson UO, Hausel J, Thorell A, Ljungqvist O, Soop M, Nygren J, et al. Adherence to the Enhanced Recovery After Surgery Protocol and Outcomes After Colorectal Cancer Surgery. *Arch Surg* (2011) 146(5):571–7. doi: 10.1001/archsurg.2010.309
18. Varadhan KK, Lobo DN. A Meta-Analysis of Randomised Controlled Trials of Intravenous Fluid Therapy in Major Elective Open Abdominal Surgery: Getting the Balance Right. *Proc Nutr Soc* (2010) 69(4):488–98. doi: 10.1017/S0029665110001734
19. Bulut O, Aslak KK, Levic K, Nielsen CB, Romer E, Sorensen S, et al. A Randomized Pilot Study on Single-Port Versus Conventional Laparoscopic Rectal Surgery: Effects on Postoperative Pain and the Stress Response to Surgery. *Tech Coloproctol* (2015) 19(1):11–22. doi: 10.1007/s10151-014-1237-6
20. Huscher CG, Mingoli A, Sgarzini G, Mereu A, Binda B, Brachini G, et al. Standard Laparoscopic Versus Single-Incision Laparoscopic Colectomy for Cancer: Early Results of a Randomized Prospective Study. *Am J Surg* (2012) 204(1):115–20. doi: 10.1016/j.amjsurg.2011.09.005

21. Kang BM, Park SJ, Lee KY, Lee SH. Single-Port Laparoscopic Surgery Can Be Performed Safely and Appropriately for Colon Cancer: Short-Term Results of a Pilot Randomized Controlled Trial. *J Laparoendosc Adv Surg Tech A* (2017) 27(5):501–9. doi: 10.1089/lap.2016.0467
22. Lee YS, Kim JH, Kim HJ, Lee SC, Kang BM, Kim CW, et al. Short-Term Outcomes of Single-Port Versus Multiport Laparoscopic Surgery for Colon Cancer: The SIMPLE Multicenter Randomized Clinical Trial. *Ann Surg* (2021) 273(2):217–23. doi: 10.1097/SLA.0000000000003882
23. Maggiori L, Tuech JJ, Cotte E, Lelong B, Denost Q, Karoui M, et al. Single-Incision Laparoscopy Versus Multiport Laparoscopy for Colonic Surgery: A Multicenter, Double-Blinded, Randomized Controlled Trial. *Ann Surg* (2018) 268(5):740–6. doi: 10.1097/SLA.0000000000002836
24. Poon JT, Cheung CW, Fan JK, Lo OS, Law WL. Single-Incision Versus Conventional Laparoscopic Colectomy for Colonic Neoplasm: A Randomized, Controlled Trial. *Surg Endosc* (2012) 26(10):2729–34. doi: 10.1007/s00464-012-2262-z
25. Watanabe J, Ota M, Fujii S, Suwa H, Ishibe A, Endo I. Randomized Clinical Trial of Single-Incision Versus Multiport Laparoscopic Colectomy. *Br J Surg* (2016) 103(10):1276–81. doi: 10.1002/bjs.10212
26. Osborne AJ, Lim J, Gash KJ, Chaudhary B, Dixon AR. Comparison of Single-Incision Laparoscopic High Anterior Resection With Standard Laparoscopic High Anterior Resection. *Colorectal Dis* (2013) 15(3):329–33. doi: 10.1111/j.1463-1318.2012.03178.x

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Surgery

CLINICAL TRIAL
published: 01 February 2022
doi: 10.3389/fsurg.2022.812343

Total Mesorectal Excision vs. Transanal Endoscopic Microsurgery Followed by Radiotherapy for T2N0M0 Distal Rectal Cancer: A Multicenter Randomized Trial

Junwei Tang†, Yue Zhang†, Dongsheng Zhang, Chuan Zhang, Kangpeng Jin, Dongjian Ji, Wen Peng, Yifei Feng* and Yueming Sun*

Colorectal Surgery Division, Department of General Surgery, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China

OPEN ACCESS

Edited by:
Ren Zhao,
Shanghai Jiao Tong University, China

Reviewed by:
Dario D'Antonio,
ASL Napoli 2 Nord, Italy
Giuditta Chiloiro,
Agostino Gemelli University Polyclinic (IRCCS), Italy

***Correspondence:**
Yueming Sun
sunyueming@njmu.edu.cn
Yifei Feng
fengyifei1982@163.com

†These authors have contributed equally to this work and share first authorship

Specialty section:
This article was submitted to Surgical Oncology, a section of the journal Frontiers in Surgery

Received: *10 November 2021*
Accepted: *10 January 2022*
Published: *01 February 2022*

Citation:
Tang J, Zhang Y, Zhang D, Zhang C, Jin K, Ji D, Peng W, Feng Y and Sun Y (2022) Total Mesorectal Excision vs. Transanal Endoscopic Microsurgery Followed by Radiotherapy for T2N0M0 Distal Rectal Cancer: A Multicenter Randomized Trial. Front. Surg. 9:812343. doi: 10.3389/fsurg.2022.812343

Introduction: Transanal endoscopic microsurgery (TEM) is an organ-preserving treatment alternative for patients with early rectal cancer. However, TEM alone is associated with greater risk of local recurrence and inferior survival in comparison with total meso-rectal excision (TME). As an important adjuvant therapy, radiotherapy can effectively reduce the local recurrence rate of rectal cancer. This study aimed to investigate whether TEM followed by radiotherapy can be a valid alternative to TME in T2N0M0 distal rectal cancer treatment.

Methods: We plan to recruit 168 participants meeting established inclusion criteria. Following informed consent, participants will randomly receive treatment protocols of TEM followed by radiotherapy (a total dose of 45–50.4 Gy given in 25–28 factions) or TME. Depending on post-operative pathology, the participants will receive either long-term follow-up or further treatment. The primary endpoint of this trial is 3-year local recurrence rate. The secondary end points include 3-year disease-free survival rate, 3-year overall survival rate, 3-year mortality rate, post-operative quality of life, post-operative safety index, intraoperative evaluation index and post-operative short-term evaluation index.

Discussion: This trial is the first prospective randomized trial to investigate the rectum preserving treatment by using transanal local excision followed by radiotherapy.

Clinical trial registration: The trial was prospectively registered at ClinicalTrials.gov NCT04098471 on September 20, 2019.

Keywords: radiotherapy, total meso-rectal excision, T2N0M0, rectal cancer, transanal endoscopic microsurgery

INTRODUCTION

Colorectal cancer (CRC) was the third most commonly diagnosed cancer and was the second leading cause of cancer-related death in the world (1). In China, CRC was also one of the most common malignant tumors, and the incidence continues to increase (2), which became a fatal health problem.

Rectal cancer accounts for more than 65% of CRC (3). In the early 1980s, Total meso-rectal excision (TME) was raised by Heald, which emphasized a sharp and meticulous dissection of the tumor and mesorectum with all associated lymph nodes through the avascular embryologic plane (4, 5). TME was considered to the most important progress in surgery for rectal cancer in the last two decades. With the application of TME, the local recurrence decreased to 6 to 12%, and 5-year survival rate improved by 53–87% (6–9). Hence, TME has gradually become a standard component of radical surgery in rectal cancer treatment (10). However, some complications, such as anastomotic leakage, anastomotic hemorrhage, anterior excision syndrome and sexual dysfunction, are common after TME, especially in distal rectal cancer treatment (11–13). Transanal local excision (TLE) is commonly used in benign neoplasms and low-risk superficial malignant rectal cancer. Transanal endoscopic microsurgery (TEM) created by Buess in 1980s, is a technique of TLE which enables the surgeon to perform a full thickness excision with great precision (14). Compared with TME, traditional TLE and TEM both have the significant advantages of preserving anorectal, sexual and urinary functions, reducing the mortality and improving the quality of life (15–17). However, lymph node dissection of rectal cancer was not involved in TLE, which leads to great concern about the increase of tumor recurrence rate and the decrease of survival rate. Although the risk of lymph node metastasis is closely related to the depth of invasion, lymph node metastasis has also been found in patients with early cancer. As reported in the literature, the incidence of lymph node metastasis could reach for 10.3% in T1 stage, 26.1% in T2 stage and 51.2% in T3 stage (18).

Adjuvant therapy for rectal cancer has made great process over the last 40 years, including the adjuvant radiotherapy (RT). Even after the development of the TME with its greatly improved local control rates, radiotherapy significantly decreased the risk of local recurrence (19). For example, the result of a randomized trial of 1,861 patients showed that the rate of local recurrence at 2 years was significantly higher in TME-only group (8.2%) than in TME+RT group (2.4%) (20). The presence of undiagnosed nodal disease, extramural vascular invasion and implantation of cancer cells are the common causes of high local recurrence rate in TLE, whereas radiotherapy can alleviate it by sterilizing the excision bed and adjacent meso-rectal lymph nodes (21). Recently, increasing evidence showed that the organ preservation strategies incorporated RT as an alternative to radical surgery for the early-stage rectal cancer (22, 23). Therefore, for better implementing the organ-preserving strategy, we hypothesized that TEM combined with radiotherapy could be safely and effectively used for the eligible T2N0M0 rectal cancer treatment. The primary objective of this study is to compare the local recurrence rate of TEM followed by radiotherapy and laparoscopic TME surgery in the treatment of T2N0M0 distal rectal cancer. Secondary objectives are long-term survival rate, intraoperative and post-operative situation, and quality of life.

METHODS

Inclusion Criteria

The inclusion criteria were as followed: (1) Subjects were 18–75 years old; (2) Pre-operative pathological diagnosis was adenocarcinoma; (3) The location of tumor was within 4 cm of anal verge; (4) Tumor size ≤3 cm; (5) The mass is mobile and non-fixed; (6) Pre-operative MRI and rectal EUS suggest that the stage was T2 only; (7) Pre-operative high-resolution CT and MRI showed no evidence of lymphatic metastasis or distant metastasis; (8) The general condition of the subjects was fair and their ASA score ≤3; (9) Subjects signed an informed consent form.

Exclusion Criteria

The exclusion criteria were as followed: (1) Participants are Suffering from other malignant tumors within 5 years; (2) Pathological type were poorly differentiated adenocarcinoma, mucinous adenocarcinoma or signet-ring cell carcinoma; (3) Participants are diagnosed as multiple primary colorectal tumors; (4) Participants are pregnant or lactating women; (5) Participants are suffering from severe mental disorders; (6) Participants have Received radiotherapy or chemotherapy already; (7) Participants are suffering from other intestinal diseases (FAP, HNPCC, ulcerative colitis or Crohn's disease); (8) Participants can't suffer abdominal surgery for various reasons; (9) Participants are involved in other clinical trials.

Exit Criteria

The exit criteria were as followed: (1) Subjects fail for the implementation of the treatment plan for various reasons; (2) The study cannot be continued due to the poor compliance of subjects; (3) Subjects request to withdraw or terminate the treatment due to personal reasons.

Design and Procedures

The study is a prospective, randomized, open and parallel controlled study to determine whether TEM followed by radiotherapy can be considered as an effective therapeutic strategy in eligible T2N0M0 rectal cancer. Firstly, all the subjects who met the inclusion criteria were randomly divided into TME group and TEM followed by radiotherapy group, treated with TME and TEM surgery, respectively. Randomization was performed by an Electronic Data Capture System (EDC) called Clinflash EDC. After histological detection of the resected specimen, subjects undergoing TEM with a pT2N0M0 adenocarcinoma, clear margin and no neurovascular invasion, will receive the post-operative RT with a total dose of 45–50.4 Gy which is given in 25–28 factions. Whereas, subjects with undergoing TME surgery will not receive any other treatment in this situation. Finally, all patients will be followed up. The flow chart of the study is shown in **Figure 1**.

End Points

The primary end point is 3-year local recurrence rate. Secondary end points include 3-year disease-free survival rate, 3-year overall survival rate, 3-year mortality rate, post-operative quality of life,

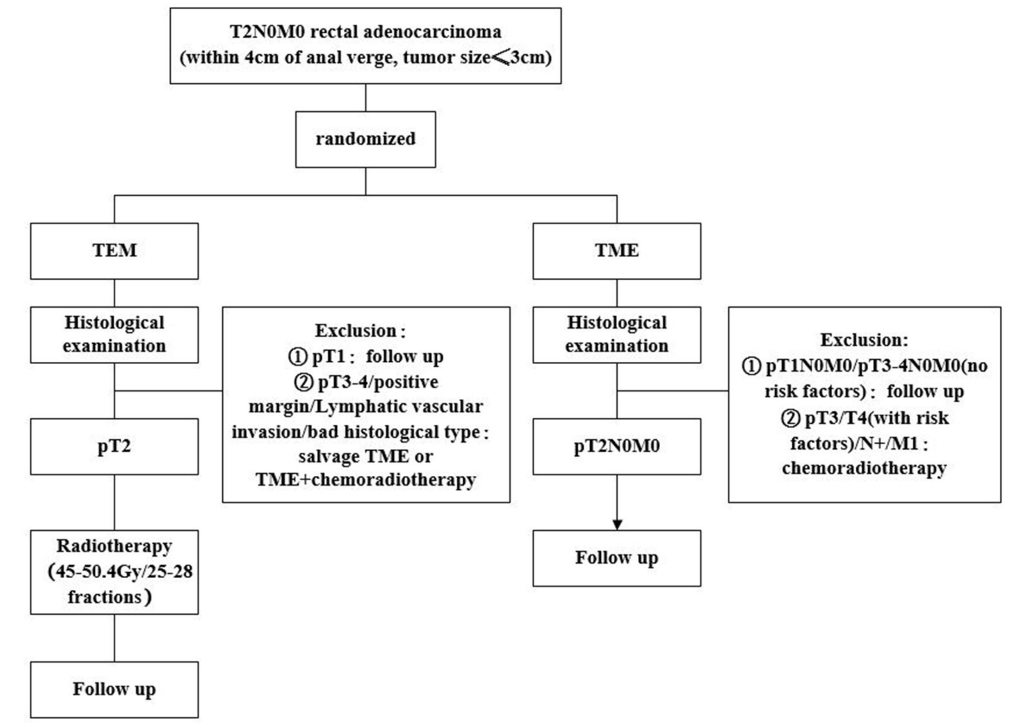


FIGURE 1 | Flowchart of the study.

post-operative safety index, intraoperative evaluation index and post-operative short-term evaluation index. Specifically, post-operative safety index includes complication rate, perioperative mortality and R0 resection rate. Intraoperative evaluation index includes operative time, intraoperative blood loss, colostomy rate and intraoperative blood transfusion. Post-operative short-term evaluation index includes intestinal exhaust time, post-operative pain and hospital stay. All subjects will be followed up in the outpatient service every 3 months for 3 years. CT scan of abdomen and thorax and colonoscopy must be performed every 6 months. Moreover, ERUS should be performed in patients treated with TEM every 3 months. EORTC QLQ-C30 & LC13 will be measured the quality of life.

Participating Centers

At least 5 Chinese hospitals will participate in the study, and all of which are experienced in laparoscopic TME and TEM surgery for rectal cancer treatment.

Sample Size Calculation

In a review of the laparoscopic TME surgery performed in our department, the 3-year recurrence free rate of T2N0M0 rectal cancer patients was nearly 95%. According to 10% of non-inferiority value, 1:1 of the sample size in two groups, 0.025 of the first type of error, 80% power and maximum 10% highest lost rate of follow-up, calculated by Pearson chi-square test, each group needs to include 84 cases, 168 cases in total.

Statistical Methods

Data collection and analysis will be performed by the SPSS 21.0, Graphpad prsim 5 and Excel software. The measurement data will be expressed as mean ± standard deviation. The statistical analyses will be performed using *t*-tests, Pearson's χ^2 tests and ANOVA. Cumulative survival analysis will be performed by the Kaplan–Meier method. Differences are considered to be statistically significant at $P \leq 0.05$.

DISCUSSION

A TME involves a complete excision of the mesorectum, including associated vascular, lymphatic structures and fatty tissue, is recommended in abdominal resections and significantly improved patients' prognosis (24). With the improvement of oncological outcome, the question has risen if new therapeutic schedule can be developed with safe efficacy and better organ preserving.

Transanal local excision, as a minimally invasive and rectum-preserving treatment, have its advantages of minimal morbidity and mortality, rapid post-operative recovery and a higher post-operative quality of life. Compared with traditional TLE, TEM may be technically feasible for more proximal lesions. A 2015 meta-analysis reported that TEM was oncologically superior to direct TLE for the excision of rectal neoplasms because of a higher rate of negative microscopic margins, a reduced rate of specimen fragmentation and lesion recurrence (25). However, due to the absence of pathologic staging of nodal involvement, the safety of TEM were still controversial for a long time (26–29). At present, TEM is only suggested to treat in selected T1N0M0 rectal cancer or patients physically unfit to undergo TME surgery based on the NCCN guidelines (30).

Although the long-term data on local resection in patients with T2N0M0 rectal cancer are limited, evidence showed that the oncological effect of TLE alone was not satisfactory for patients with T2N0M0 rectal cancer (23, 28, 31, 32). For example, a retrospective study of 1,030 patients showed the 5-year local recurrence rates of T2 tumors increased and the 5-year overall survival decreased after TLE compared to standard resection (31). Even though some reports supported the application of TEM in the treatment of T2 rectal cancer (26, 27), its safety is still worrying (33, 34). For better applying TEM to the treatment of T2N0M0 rectal cancer, TEM combined with adjuvant therapy have been carried out in recent years (35–37). For example, in a prospective multicenter trial named CARTS study (38, 39), patients with a clinical T1-3N0M0 rectal adenocarcinoma were treated with chemoradiation therapy (CRT) for reaching a near pCR, then TEM were performed in patients with good response. The result of 55 patients showed CRT enables organ preservation with additional TEM surgery in approximately two-thirds of patients with good long-term oncological outcome in cT1-3N0M0 rectal cancer. In another prospective multi-institutional trial (40), patients with T2N0M0 rectal cancer were treated with neoadjuvant chemoradiotherapy followed by local excision, the result of 79 patients showed that 3-year disease-free survival and overall survival were 88 and 95%, respectively, suggesting that CRT followed by TLE could be considered as an organ-preserving alternative in selected patients with T2N0M0 rectal cancer. All these findings allow the possibility of saving the rectum by the treatment modality of TEM after neoadjuvant chemoradiotherapy in patients with T2N0M0 rectal cancer. However, many patients cannot accept the strategy of TEM after neoadjuvant chemoradiotherapy and were dying to receive surgical treatment as soon as possible. Additionally, chemoradiotherapy followed by TEM possibly led to a high incidence of complications and gave rise to cumulative toxicities that detract from the benefits of organ preservation (39–42). The strategy of TEM combined with post-operative radiotherapy should be further considered.

Due to the function of adjuvant radiotherapy in sterilizing subclinical mesorectal lymph nodes and the excision bed, the treatment strategy with TLE followed by radiotherapy may be a valid alternative to TME in T2N0M0 rectal cancer (43). In a mutilative analyses of 3,786 patients base on the SEER database (23), survival rates were analyzed between local excision (LE) alone, LE followed by radiotherapy and major resection (MR). The results suggested that the 5-year cancer specific survival rate and 5-year overall survival rate were significantly higher in MR group than those in LE alone group, but similar with those in LE followed by radiotherapy group. However, data is limited and only a few small retrospective studies have reported in this field. To date, there is no prospective randomized study to prove the feasibility of LE followed by radiotherapy in patients with T2N0M0 rectal cancer, further studies are needed in this field.

The trial compared the long-term efficacy of TEM followed by radiotherapy and TME for patients with T2N0M0 rectal cancer, which is the first prospective randomized study in the area. This study will provide strong evidence whether this rectum saving strategy for the treatment of rectal cancer is feasible.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YS, YF, and JT conceived and designed the initial project. The protocol was drafted by YZ, which was modified by DZ, CZ, KJ, DJ, and WP. All authors have read and approved the final study protocol.

FUNDING

The authors appreciate the help of all participants that are taking part in the study and the support by Jiangsu Provincial social development key project (BE2021742). Jiangsu Provincial Natural Science Foundation for Basic Research (Grant No. BK20201491), Jiangsu Key Medical Discipline (General Surgery, Grant No. ZDxKA2016005), and the National Key R&D Program of China (Grant No. 2017YFC0908200).

REFERENCES

1. Erratum: global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. (2020) 70:313. doi: 10.3322/caac.21609
2. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, et al. Cancer statistics in China, 2015. *CA Cancer J Clin*. (2016) 66:115–32. doi: 10.3322/caac.21338
3. Hamstra DA, Stenmark MH, Ritter T, Litzenberg D, Jackson W, Johnson S, et al. Age and comorbid illness are associated with late rectal toxicity following dose-escalated radiation therapy for prostate cancer. *Int J Radiat Oncol Biol Phys*. (2013) 85:1246–53. doi: 10.1016/j.ijrobp.2012.10.042
4. Heald RJ. The 'Holy Plane' of rectal surgery. *J R Soc Med*. (1988) 81:503–8. doi: 10.1177/014107688808100904
5. Knol J, Keller DS. Total mesorectal excision technique-past, present, and future. *Clin Colon Rectal Surg*. (2020) 33:134–43. doi: 10.1055/s-0039-3402776
6. Salomonsson M, Skott O, Persson AE. Lack of effect of intraluminal pressure on renin release from isolated afferent arterioles. *Pflugers Arch*. (1992) 421:466–8. doi: 10.1007/BF00370257

7. Ross A, Rusnak C, Weinerman B, Kuechler P, Hayashi A, MacLachlan G, et al. Recurrence and survival after surgical management of rectal cancer. *Am J Surg*. (1999) 177:392–5. doi: 10.1016/S0002-9610(99)00080-X
8. Hill GL, Rafique M. Extrafascial excision of the rectum for rectal cancer. *Br J Surg*. (1998) 85:809–12. doi: 10.1046/j.1365-2168.1998.00735.x
9. Bjerkeset T, Edna TH. Rectal cancer: the influence of type of operation on local recurrence and survival. *Eur J Surg*. (1996) 162:643–8.
10. Gopall J, Shen XF, Cheng Y. Current status of laparoscopic total mesorectal excision. *Am J Surg*. (2012) 203:230–41. doi: 10.1016/j.amjsurg.2011.03.011
11. Keating JP Sexual function after rectal excision. ANZ J Surg. (2004) 74:248–259. doi: 10.1111/j.1445-2197.2004.02954.x
12. Kim SH, Park IJ, Joh YG, Hahn KY. Laparoscopic resection for rectal cancer: a prospective analysis of thirty-month follow-up outcomes in 312 patients. *Surg Endosc*. (2006) 20:1197–202. doi: 10.1007/s00464-005-0599-2
13. Park JS, Choi GS, Kim SH, Kim HR, Kim NK, Lee KY, et al. Multicenter analysis of risk factors for anastomotic leakage after laparoscopic rectal cancer excision: the Korean laparoscopic colorectal surgery study group. *Ann Surg*. (2013) 257:665–71. doi: 10.1097/SLA.0b013e31827b8ed9
14. Buess G, Hutterer F, Theiss J, Bobel M, Isselhard W, Pichlmaier H. [A system for a transanal endoscopic rectum operation]. *Chirurg*. (1984) 55:677–80.
15. Lartigau C, Lebreton G, Alves A. Local resection for small rectal cancer. *J Visc Surg*. (2013) 150:325–31. doi: 10.1016/j.jviscsurg.2013.08.004
16. Althumairi AA, Gearhart SL. Local excision for early rectal cancer: transanal endoscopic microsurgery and beyond. *J Gastrointest Oncol*. (2015) 6:296–306. doi: 10.3978/j.issn.2078-6891.2015.022
17. Smart CJ, Cunningham C, Bach SP. Transanal endoscopic microsurgery. *Best Pract Res Clin Gastroenterol*. (2014) 28:143–57. doi: 10.1016/j.bpg.2013.11.005
18. Hashiguchi Y, Muro K, Saito Y, Ito Y, Ajioka Y, Hamaguchi T, et al. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2019 for the treatment of colorectal cancer. *Int J Clin Oncol*. (2020) 25:1–42. doi: 10.1007/s10147-019-01485-z
19. Ramsey S, Tepper JE. Rectal cancer radiotherapy. *Cancer J*. (2007) 13:204–9. doi: 10.1097/PPO.0b013e318074def2
20. Tiefenbacher U, Wenz F. [Pre-operative radiotherapy combined with total mesorectal excision for resectable rectal cancer]. *Strahlenther Onkol*. (2001) 177:682–4. doi: 10.1056/NEJMoa010580
21. Jones HJS, Goodbrand S, Hompes R, Mortensen N, Cunningham C. Radiotherapy after local excision of rectal cancer may offer reduced local recurrence rates. *Colorectal Dis*. (2019) 21:451–9. doi: 10.1111/codi.14546
22. Sasaki T, Ito Y, Ohue M, Kanemitsu Y, Kobatake T, Ito M, et al. Postoperative chemoradiotherapy after local resection for high-risk T1 to T2 low rectal cancer: results of a single-arm, multi-institutional, phase II clinical trial. *Dis Colon Rectum*. (2017) 60:914–21. doi: 10.1097/DCR.0000000000000870
23. Wang XJ, Chi P, Zhang YY, Lin HM, Lu XR, Huang Y, et al. Survival outcome of adjuvant radiotherapy after local excision for T2 early rectal cancer: an analysis based on the surveillance, epidemiology, and end result registry database. *Eur J Surg Oncol*. (2018) 44:1865–72. doi: 10.1016/j.ejso.2018.08.024
24. Delibegovic S. Introduction to total mesorectal excision. *Med Arch*. (2017) 71:434–8. doi: 10.5455/medarh.2017.71.434-438
25. Clancy C, Burke JP, Albert MR, O'Connell PR, Winter DC. Transanal endoscopic microsurgery versus standard transanal excision for the removal of rectal neoplasms: a systematic review and meta-analysis. *Dis Colon Rectum*. (2015) 58:254–61. doi: 10.1097/DCR.0000000000000309
26. Lezoche G, Guerrieri M, Baldarelli M, Paganini AM, D'Ambrosio G, Campagnacci R, et al. Transanal endoscopic microsurgery for 135 patients with small nonadvanced low rectal cancer (iT1-iT2, iN0): short- and long-term results. *Surg Endosc*. (2011) 25:1222–9. doi: 10.1007/s00464-010-1347-9
27. Lezoche E, Baldarelli M, De Sanctis A, Lezoche G, Guerrieri M. Early rectal cancer: definition and management. *Dig Dis*. (2007) 25:76–9. doi: 10.1159/000099173
28. Elmessiry MM, Van Koughnett JA, Maya A, DaSilva G, Wexner SD, Bejarano P, et al. Local excision of T1 and T2 rectal cancer: proceed with caution. *Colorectal Dis*. (2014) 16:703–9. doi: 10.1111/codi.12657
29. De Graaf EJ, Doornebosch PG, Tollenaar RA, Meershoek-Klein Kranenbarg E, de Boer AC, Bekkering FC, et al. Transanal endoscopic microsurgery versus total mesorectal excision of T1 rectal adenocarcinomas with curative intention. *Eur J Surg Oncol*. (2009) 35:1280–5. doi: 10.1016/j.ejso.2009.05.001
30. Willett CG, Compton CC, Shellito PC, Efird JT. Selection factors for local excision or abdominoperineal resection of early stage rectal cancer. *Cancer*. (1994) 73:2716–20.
31. You YN, Baxter NN, Stewart A, Nelson H. Is the increasing rate of local excision for stage I rectal cancer in the United States justified?: a nationwide cohort study from the National Cancer Database. *Ann Surg*. (2007) 245:726–33. doi: 10.1097/01.sla.0000252590.95116.4f
32. Veereman G, Vlayen J, Robays J, Fairon N, Stordeur S, Rolfo C, et al. Systematic review and meta-analysis of local resection or transanal endoscopic microsurgery versus radical resection in stage i rectal cancer: a real standard? *Crit Rev Oncol Hematol*. (2017) 114:43–52. doi: 10.1016/j.critrevonc.2017.03.008
33. Chiniah M, Ganganah O, Cheng Y, Sah SK. Transanal endoscopic microsurgery is an oncologically safe alternative to total mesorectal excision for stage I rectal cancer: results of a meta-analysis of randomized controlled trials. *Int J Colorectal Dis*. (2016) 31:1501–4. doi: 10.1007/s00384-016-2530-9
34. Stornes T, Wibe A, Nesbakken A, Myklebust TA, Endreseth BH. National early rectal cancer treatment revisited. *Dis Colon Rectum*. (2016) 59:623–9. doi: 10.1097/DCR.0000000000000591
35. Perez RO, Habr-Gama A, Lynn PB, Sao Juliao GP, Bianchi R, Proscurshim I, et al. Transanal endoscopic microsurgery for residual rectal cancer (ypT0-2) following neoadjuvant chemoradiation therapy: another word of caution. *Dis Colon Rectum*. (2013) 56:6–13. doi: 10.1097/DCR.0b013e318273f56f
36. Allaix ME, Arezzo A, Giraudo G, Morino M. Transanal endoscopic microsurgery vs. laparoscopic total mesorectal excision for T2N0 rectal cancer. *J Gastrointest Surg*. (2012) 16:2280–7. doi: 10.1007/s11605-012-2046-8
37. Lezoche E, Baldarelli M, Lezoche G, Paganini AM, Gesuita R, Guerrieri M. Randomized clinical trial of endoluminal locoregional resection versus laparoscopic total mesorectal excision for T2 rectal cancer after neoadjuvant therapy. *Br J Surg*. (2012) 99:1211–8. doi: 10.1002/bjs.8821
38. Bokkerink GM, de Graaf EJ, Punt CJ, Nagtegaal ID, Rutten H, Nuyttens JJ, et al. The CARTS study: chemoradiation therapy for rectal cancer in the distal rectum followed by organ-sparing transanal endoscopic microsurgery. *BMC Surg*. (2011) 11:34. doi: 10.1186/1471-2482-11-34
39. Stijns RCH, de Graaf EJR, Punt CJA, Nagtegaal ID, Nuyttens J, van Meerten E, et al. Long-term oncological and functional outcomes of chemoradiotherapy followed by organ-sparing transanal endoscopic microsurgery for distal rectal cancer: the CARTS study. *JAMA Surg*. (2019) 154:47–54. doi: 10.1001/jamasurg.2018.3752
40. Garcia-Aguilar J, Renfro LA, Chow OS, Shi Q, Carrero XW, Lynn PB, et al. Organ preservation for clinical T2N0 distal rectal cancer using neoadjuvant chemoradiotherapy and local excision (ACOSOG Z6041): results of an open-label, single-arm, multi-institutional, phase 2 trial. *Lancet Oncol*. (2015) 16:1537–46. doi: 10.1016/S1470-2045(15)00215-6
41. Arezzo A, Arolfo S, Allaix ME, Munoz F, Cassoni P, Monagheddu C, et al. Results of neoadjuvant short-course radiation therapy followed by transanal endoscopic microsurgery for t1-t2 n0 extraperitoneal rectal cancer. *Int J Radiat Oncol Biol Phys*. (2015) 92:299–306. doi: 10.1016/j.ijrobp.2015.01.024
42. Rullier E, Vendrely V, Asselineau J, Rouanet P, Tuech JJ, Valverde A, et al. Organ preservation with chemoradiotherapy plus local excision for rectal cancer: 5-year results of the GRECCAR 2 randomised trial. *Lancet Gastroenterol Hepatol*. (2020) 5:465–74. doi: 10.1016/S2468-1253(19)30410-8
43. Gopaul D, Belliveau P, Vuong T, Trudel J, Vasilevsky CA, Corns R, et al. Outcome of local excision of rectal carcinoma.

Dis Colon Rectum. (2004) 47:1780–8. doi: 10.1007/s10350-004-0678-9

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

ORIGINAL RESEARCH
published: 22 April 2022
doi: 10.3389/fonc.2022.853662

Check for updates

Significance of Nerve Plane for Inferior Mesenteric Plexus Preservation in Laparoscopic Rectal Cancer Surgery

Kai Li[1], *Junjie Zeng*[1], *Pengcheng Pang*[1], *Hua Cheng*[1], *Xiaobo He*[1], *Fengyu Cao*[1], *Qiang Luo*[2], *Shilun Tong*[1] *and Yongbin Zheng*[1*]

[1] Department of Gastrointestinal Surgery, Renmin Hospital of Wuhan University, Wuhan, China, [2] Division of Nephrology, Renmin Hospital of Wuhan University, Wuhan, China

Edited by:
Ren Zhao,
Shanghai Jiao Tong University,
China

Reviewed by:
Francesco Bianco,
Ospedale San Leonardo ASLNA3,
Italy
Haitao Zhou,
Chinese Academy of
Medical Sciences and Peking Union
Medical College, China

***Correspondence:**
Yongbin Zheng
yongbinzheng@whu.edu.cn

Specialty section:
This article was submitted to
Surgical Oncology,
a section of the journal
Frontiers in Oncology

Received: 12 January 2022
Accepted: 18 March 2022
Published: 22 April 2022

Citation:
Li K, Zeng J, Pang P, Cheng H, He X, Cao F, Luo Q, Tong S and Zheng Y (2022) Significance of Nerve Plane for Inferior Mesenteric Plexus Preservation in Laparoscopic Rectal Cancer Surgery. Front. Oncol. 12:853662. doi: 10.3389/fonc.2022.853662

Background: Station 253 node dissection with high ligation of the inferior mesenteric artery (IMA) is difficult to perform without damage to the surrounding autonomic nerve plexuses. This study aimed to investigate the significance of the nerve plane for inferior mesenteric plexus (IMP) preservation in laparoscopic rectal cancer surgery.

Methods: A total of 56 consecutive rectal patients underwent laparoscopic en bloc station 253 node dissection with high ligation of the IMA. Station 253 nodes were divided into the extra- and intra-nerve plane station 253 nodes for further H&E staining and immunohistochemical analysis. Based on IMP nerve plane-based evidence and histopathological results, a novel nerve-sparing technique, IMP nerve plane orientation, was proposed and performed on 68 rectal cancer patients. Urinary and sexual functions in all patients were evaluated at 6 months postoperatively.

Results: Lymph node metastasis was not found, but abundant nerve bundles containing gangliocytes were observed in extra-nerve plane station 253 nodes. The nerve plane was identified intraoperatively and then confirmed by both postoperative gross specimen evaluation and histopathological analysis. The novel nerve-sparing technique (IMP nerve plane orientation) was successfully performed with no postoperative complications, and the operated patients had improved postoperative urinary and sexual functions.

Conclusion: The nerve plane is helpful for IMP preservation and station 253 node dissection. This novel nerve-sparing technique of nerve plane orientation is technically feasible and safe, which could result in faster recovery of urinary and sexual functions.

Keywords: nerve plane, inferior mesenteric plexus, laparoscopic surgery, rectal cancer, station 253 node

INTRODUCTION

The Japanese criteria practically define station 253 nodes as nodes that lie along the inferior mesenteric artery (IMA) from the origin of the left colic artery (LCA) to the origin of the IMA (1). The incidence of station 253 node metastasis is relatively low, i.e., approximately 0.3% to 8.6%, in different tumor stages (2). Station 253 node metastasis is more likely to occur in locally advanced rectal cancer above the peritoneal reflection (3); besides, en bloc station 253 node dissection is technically demanding and carries a risk of damage to the surrounding inferior mesenteric plexus (IMP), which may be associated with postoperative organ dysfunction, including urinary and sexual dysfunctions (4, 5). However, station 253 node metastasis is an important prognostic factor of rectal cancer. Therefore, whether en bloc station 253 node dissection is suitable for all rectal cancer patients remains controversial. Moreover, the current definition of station 253 nodes is limited to around the IMA, which is vague, and there is no consistent evidence about the clear border of the area of station 253 nodes.

The nerve plane was defined as the overlying tiny membranous tissue including the nerve, the adipose tissue, and extremely tiny capillaries around the nerve, as described in our previous studies (6–8). Similarly, there is still the IMP nerve plane around the IMA, which divides routine station 253 nodes into extra- and intra-nerve plane station 253 nodes. In the present study, we hypothesized that the nerve plane is the dorsal boundary of station 253 nodes, which should be preserved during station 253 node dissection; intra-nerve plane station 253 nodes are regional lymph nodes, which should be cleaned; and extra-nerve plane station 253 nodes are extra-mesenteric lymph nodes, which are unnecessarily cleaned. We believe that intraoperative IMP nerve plane preservation not only ensures that intra-mesenteric regional lymph nodes are cleaned totally but also better prevents damage to pelvic autonomic nerves. Therefore, the IMP nerve plane is clinically important in IMP preservation and station 253 node dissection in laparoscopic surgery for rectal cancer.

Therefore, the present study aimed to investigate the significance of the nerve plane for IMP preservation in laparoscopic rectal cancer surgery and to propose a novel nerve-sparing technique of nerve plane orientation for station 253 node dissection.

MATERIALS AND METHODS

A total of 124 rectal cancer patients were enrolled in this study; patients were divided into a nerve plane-oriented group and a no nerve plane-oriented group. From October 2019 to June 2020, a total of 56 rectal cancer patients in the no nerve plane-oriented group undergoing laparoscopic radical resection with en bloc station 253 node dissection in the Department of Gastrointestinal Surgery, Renmin Hospital of Wuhan University, were prospectively enrolled. Pelvic autonomic nerves including the IMP were preserved as much as possible, although en bloc station 253 nodes were cleaned. The IMP nerve plane was intraoperatively identified, and the routine station 253 nodes were divided into extra- and intra-nerve plane nodes (**Figure 1**). These lymph node tissues were dehydrated, paraffin embedded, cut into 5-μm sections, and processed for H&E staining. In addition, immunohistochemistry was performed to identify autonomic nerve fibers. Neuronal immunolabeling was performed with anti-rabbit Protein S100 antibodies (S100, 1:400; Abcam, Cambridge, MA, USA). S100 is a general immunolabeling marker of all nerves, which can specifically identify the nucleus and cytoplasm of Schwann cells in formalin-fixed paraffin-embedded nerve tissue specimens.

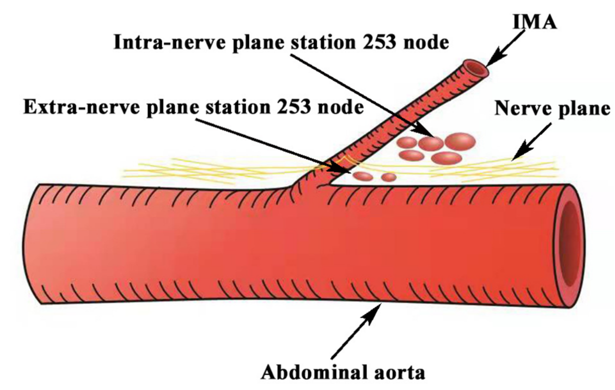


FIGURE 1 | Schematic representation of the extra- and intra-nerve plane station 253 nodes. Station 253 nodes were divided into the extra- and intra-nerve plane station 253 nodes by the IMP nerve plane. IMA, inferior mesenteric artery; IMP, inferior mesenteric plexus.

Based on IMP nerve plane-based evidence and histopathological examination, a novel nerve-sparing technique of nerve plane orientation for IMP preservation was performed on 68 rectal cancer patients in the nerve plane-oriented group between July 2020 and February 2021. Extra-nerve plane station 253 nodes were preserved, and intra-nerve plane station 253 nodes were cleaned and examined by H&E and immunohistochemical (S100) staining. All operations were performed by Prof. Yongbin Zheng, a chief physician of the Department of Gastrointestinal Surgery, Renmin Hospital of Wuhan University, with a 20-year post-certification experience performing approximately 350 cases of laparoscopic rectal cancer radical resection annually. Patient baseline data, tumor characteristics, and surgical outcomes were recorded, and all operative procedures were videotaped. Informed consent was obtained from all participating patients. This study was approved by the Institutional Review Board of Renmin Hospital, Wuhan University (no. WDRY2021-K126).

Assessment of Sexual and Urinary Functions

The urinary function was evaluated by the International Prostate Symptom Score (IPSS) questionnaire (9). IPSS total score ranged from 0 to 35: the higher the score, the severer the urinary dysfunction. Moderate-to-severe urinary dysfunction was defined as an IPSS score >8 points (10). Male sexual function was evaluated by the 5-item version of the International Index of Erectile Function (IIEF-5) (11) questionnaire and ejaculation function grading. IIEF-5's total score ranged from 1 to 25: the lower the score, the severer the erectile dysfunction. Male erectile dysfunction was defined as an IIEF-5 score ≤11 points. Ejaculation was functionally classified as follows: grade I, normal ejaculation; grade II, retrograde ejaculation; and grade III, anejaculation. Ejaculation dysfunction was identified as grade II or III ejaculation in this study (12). Female sexual function was evaluated by the Female Sexual Function Index (FSFI) system, which is a validated questionnaire comprised of 19 items. FSFI's total score ranged from 2 to 36; the higher the score, the severer the sexual dysfunction (13). Female sexual dysfunction was defined as an FSFI score <26.55 points in this study (14). Urinary and sexual functions were evaluated before surgery and at 6 postoperative months.

Statistical Analysis

Data were presented as mean (± SD) and number (frequency, %) for continuous and categorical variables, respectively. Dichotomous clinical variables were assessed by a chi-square test. Two-sided $p < 0.05$ was considered statistically significant. All statistical analyses were performed with SPSS version 20.0 (IBM, Armonk, New York, NY, USA).

RESULTS

Clinical Characteristics

A total of 124 rectal cancer patients were evaluated in this study. All participating patients received laparoscopic radical resection without conversion. Patient clinical characteristics are shown in **Table 1**. Variables, including age, sex, body mass index (BMI), prostatic hyperplasia or not, tumor location, tumor differentiation, pathological TNM stage, intra-nerve plane station 253 nodes retrieved, and total lymph nodes retrieved, had no significant differences between the two groups. Patients in the nerve plane-oriented group had reduced operative blood loss (49.6 ± 13.6 vs. 22.6 ± 13.7, $p < 0.001$) but longer operative time (165.2 ± 20.6 vs. 175 ± 25.7, $p = 0.016$) compared with patients in the no nerve plane-oriented group.

Nerve Plane and Lymph Nodes

In all patients, the typical structural features of the nerve plane were observed, as shown in **Supplementary Video 1**. The "Holy plane" was revealed more clearly in the anterior of the abdominal aorta by enforcing traction and anti-traction, and the IMP was lifted by the IMA as a "tent" when the extension was closed to the root of the IMA; the IMP was surrounded by the adipose tissue and extremely tiny capillaries and covered by a tiny membranous tissue, i.e., the IMP nerve plane (**Figure 2A**). Similarly, the abdominal aortic plexus and superior hypogastric plexus nerve planes were also observed. These nerve planes are continuous and form a novel landmark for pelvic autonomic nerve protection in laparoscopic rectal cancer surgery. Station 253 nodes within the nerve plane are called intra-nerve plane station 253 nodes, which should be cleaned in rectal cancer surgery; conversely, station 253 nodes beyond the nerve plane are called extra-nerve plane lymph nodes, which are rarely involved in tumor metastasis due to the protective effect of the nerve plane (**Figure 2B**). Subsequently, en bloc station 253 nodes were marked and divided into extra- and intra-nerve plane nodes after the specimen was removed (**Figure 2C**), which were sent to a pathological lab for further examination. Eventually, the mean number of intra-nerve plane station 253 nodes retrieved was 3.0 (range, 0–7), and 5 cases (5/56 = 8.9%) with intra-nerve plane station 253 node metastasis were confirmed by H&E staining. The mean number of extra-nerve plane station 253 nodes retrieved was 1.5 (range, 0–4), and no metastatic extra-nerve plane station 253 nodes were found. In the nerve plane-oriented group, the mean number of intra-nerve plane station 253 nodes retrieved was 3.1 (range, 1–6), and 6 cases (6/68 = 8.8%) showed intra-nerve plane station 253 node metastasis, as shown in **Table 1**.

TABLE 1 | Clinical and pathological characteristics of participating patients.

Variable	No nerve plane-oriented group (N = 56)	Nerve plane-oriented group (N = 68)	*p*
Age, mean ± SD	58.9 ± 8.4	56.0 ± 8.6	0.067
Sex (male/female)	31/25	35/33	0.666
Body mass index, kg/m^2, mean ± SD	24.3 ± 2.4	25.2 ± 3.1	0.054
History of prostatic hyperplasia, n (%)	3 (5.4%)	2 (2.9%)	0.496
Tumor site, n (%)			0.587
Above peritoneal reflexes	34 (60.7%)	38 (55.9%)	
Below peritoneal reflexes	22 (39.3%)	30 (44.1%)	
Tumor differentiation, n (%)			0.425
Well or moderate	40 (71.4%)	44 (64.7%)	
Poor, mucinous or signet-ring cell	16 (28.6%)	24 (35.3%)	
Pathological TNM stage*, n (%)			0.835
I	14 (25.0%)	14 (20.6%)	
II	29 (51.8%)	38 (55.9%)	
III	13 (23.2%)	16 (23.5%)	
Estimated blood loss, ml, mean ± SD	49.6 ± 13.6	22.6 ± 13.7	0.000
Total operative time, min, mean ± SD	165.2 ± 20.6	175 ± 25.7	0.016
Intra-nerve plane station 253 node retrieved, mean	3.0 ± 1.4	3.1 ± 1.2	0.707
Positive intra-nerve plane station 253 nodes, n (%)	5 (8.9%)	6 (8.8%)	0.984
Extra-nerve plane station 253 nodes retrieved, mean	1.5 ± 0.8		
Positive extra-nerve plane station 253 nodes, n (%)	0		
Total lymph nodes retrieved, mean ± SD	20.7 ± 6.4	22.2 ± 8.9	0.299
Total positive lymph nodes, n (%)	13 (23.2%)	16 (23.5%)	0.967

SD, standard deviation.

**TNM stage according to the American Joint Committee on Cancer, 7th ed.*

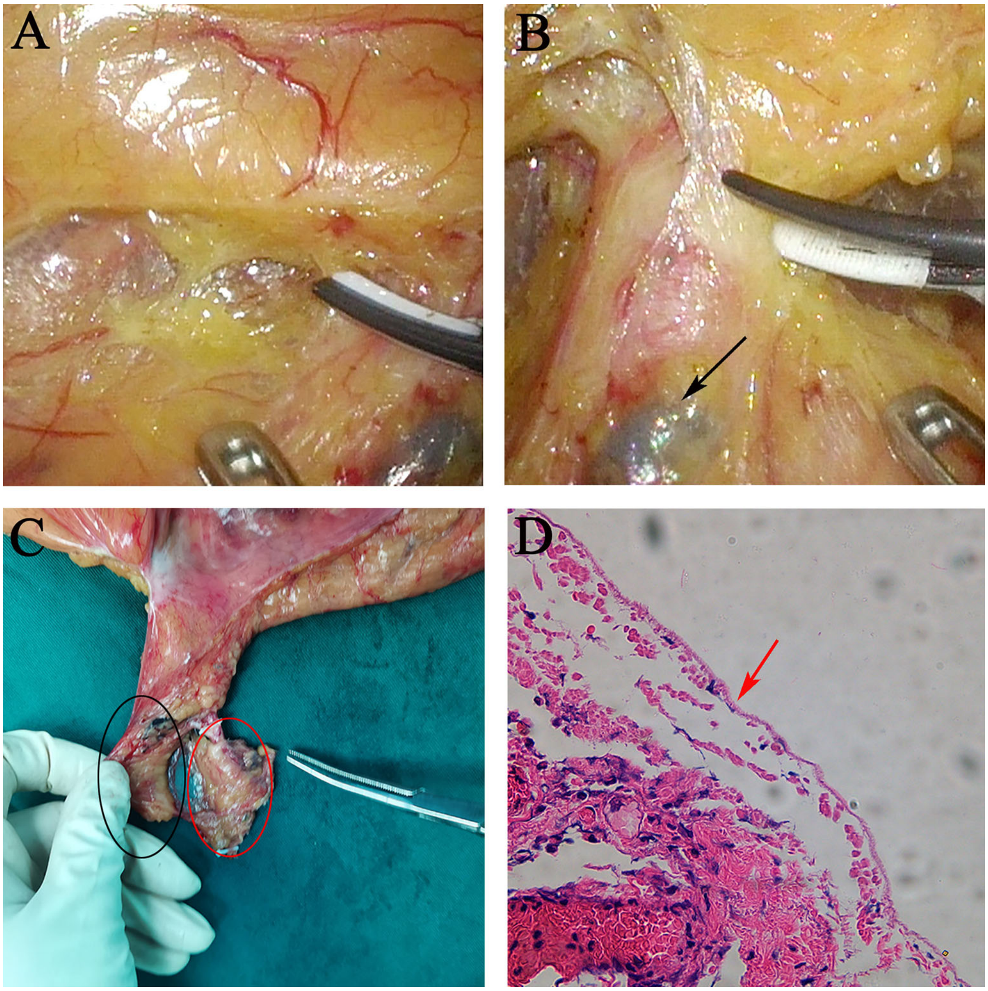


FIGURE 2 | Relationship between extra- and intra-nerve plane station 253 nodes. **(A)** Inferior mesenteric plexus nerve plane. The IMP was surrounded by the adipose tissue and extremely tiny capillaries and covered by a tiny membranous tissue. **(B)** Extra-nerve plane station 253 nodes were black-dyed by carbon nanoparticles. **(C)** Postoperative gross specimen of en bloc station 253 nodes. Black and red ovals show intra- and extra-nerve plane station 253 nodes, respectively. **(D)** H&E staining showing completely excised mesorectum of intra-nerve plane station 253 nodes; no nerve bundles were found in intra-nerve plane station 253 nodes. IMA, inferior mesenteric artery; IMP, inferior mesenteric plexus.

Histopathological Results

Nerve fibers positively stained for S100 were deep brown, and nerve bundles containing gangliocytes were observed in extra-nerve plane station 253 nodes (**Figure 3**). No nerve bundles were found in intra-nerve plane station 253 nodes, and the mesorectum in postoperative specimens was intact as shown by H&E staining (**Figure 2D**).

Nerve Plane-Based Surgical Technique

Based on the above nerve plane-based evidence and histopathological results, a novel nerve-sparing technique of nerve plane orientation was proposed. The details of the surgical procedure are shown in **Supplementary Video 2**. Briefly, dissection above the abdominal aortic plexus nerve plane was performed and extended up to the lower edge of the duodenum and down to the entrance of the IMP nerve plane (**Figure 4A**). After extension from the superior hypogastric plexus nerve plane to the IMP nerve plane posterior to the IMA (**Figure 4B**), dissection was continued over the IMP nerve plane from caudal to cephalic by the "slope climbing" approach. After crossing the IMA, dissection was continued from cephalic to caudal by the "slope downhill" approach, and the abdominal aortic plexus nerve plane was gradually entered (**Figure 4C**). Finally, the IMA was ligated and cut above the IMP nerve plane (**Figure 4D**). After a specimen was collected, the nerve plane around the IMA showed preserved integrity.

Urinary and Sexual Functions

As shown in **Table 2**, there were no significant differences in IPSS (4.3 ± 2.9 vs. 5.2 ± 2.5, $p = 0.062$), IIEF-5 (16.5 ± 3.4 vs. 17.7 ± 3.7, $p = 0.132$), and FSFI (29.2 ± 3.8 vs. 29.5 ± 3.7, $p = 0.638$) scores before surgery between the two groups. Patients in the nerve plane-

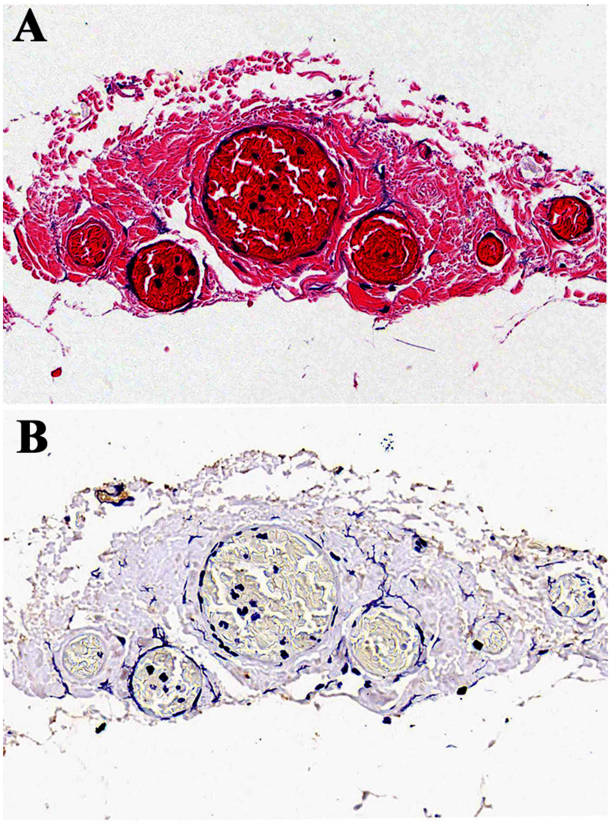


FIGURE 3 | H&E and immunohistochemical staining (S100) of extra-nerve plane station 253 nodes. **(A)** H&E staining of extra-nerve plane station 253 nodes. **(B)** Immunohistochemical staining of extra-nerve plane station 253 nodes with anti-S100 antibodies. Abundant nerve fibers positively stained for S100 were deep brown and observed in extra-nerve plane station 253 nodes.

oriented group showed higher IIEF-5 (13.9 ± 3.1 vs. 15.8 ± 3.7, p = 0.015) and FSFI (24.6 ± 4.6 vs. 27.7 ± 3.1, p = 0.006) scores than those in the no nerve plane-oriented group, although IPSS scores (6.4 ± 4.7 vs. 6.0 ± 3.4, p = 0.635) showed no significant difference between the two groups at 6 postoperative months.

There were no significant differences in urinary (8.9% vs. 7.3%, p = 0.748) and sexual (12.5% vs. 13.2%, p = 0.903) dysfunction rates before surgery between the two groups. However, patients in the nerve plane-oriented group had lower urinary (26.8% vs. 11.7%, p = 0.032) and sexual (35.7% vs. 19.1%, p = 0.037) dysfunction rates than those in the no nerve plane-oriented group at 6 postoperative months. Therefore, the patients who underwent the nerve-sparing technique of nerve plane orientation had better postoperative urinary and sexual functions.

DISCUSSION

With the introduction of total mesorectal excision (TME) surgery, rectal cancer prognosis has been greatly improved; however, the quality of life of patients after surgery has not been paid enough attention to by surgeons, which includes urinary, sexual, and bowel dysfunctions related to intraoperative pelvic autonomic nerve injury. Therefore, preserving the pelvic autonomic nerve, including IMP preservation, in rectal cancer surgery has become increasingly important. Many studies have found that station 253 node metastasis is an important prognostic factor in patients with colorectal cancer (15–17). Many consensus opinions, including the Japanese Society for Cancer of the Colon and Rectum (JSCCR) and The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines, recommended station 253 node dissection and high ligation of the IMA in rectal cancer patients with preoperative clinical $T_{2-4}N_{+}$ stage (18, 19). However, high ligation of the IMA and station 253 node dissection in laparoscopic anterior resection for rectal cancer increase the risk of IMP damage and result in postoperative urinary and sexual dysfunctions. Therefore, how to improve surgical techniques for IMP preservation is essential and represents a technical challenge for most surgeons; surgical techniques for IMP preservation are still lacking.

In the present study, the nerve plane was used as an optimal surgical landmark for laparoscopic rectal surgery, for several potential reasons. First, pelvic autonomic nerves, including the IMP, are located outside the mesorectal plane (20, 21); therefore, this technique should theoretically have consistent oncologic outcomes with routine nerve-sparing surgery. Second, not only the nerves but also the continuous nerve plane covered with the membranous tissue are preserved; thus, it could reduce intraoperative damage to pelvic autonomic nerves due to heat conduction and physicochemical factors such as wound exudate and inflammatory mediators. Finally, the nerves were not intentionally exposed during the operation, which differs from other nerve-sparing techniques such as nerve-guided technique (22, 23), active exposure of the nerve could increase nerve stretching and the risk of nerve damage. The nerve-sparing technique of nerve plane orientation for IMP preservation has been a standardized laparoscopic procedure in our institution since 2013, with satisfactory postoperative urinary and sexual functions despite the lack of follow-up for survival prognosis.

Currently, numerous studies have proposed various nerve-sparing techniques for IMP preservation. Liang et al. (24) recommended that the IMP should be preserved by sparing the pre-aortic connective tissue and leaving a 1- to 2-cm-long stump of the IMA *in situ*, consistent with most nerve-sparing techniques (25, 26). Huscher et al. (27) reported a clear identification of the branches climbing around the IMA with the Cavitron ultrasonic surgical aspirator for IMP preservation; while performing a high ligation, this nerve-sparing technique relies more on advanced medical devices than surgical technology. Sun et al. (28) also reported three anatomical levels, including the parietal fascia, the neurofascial layer, and the mesosigmoid, for IMP preservation in laparoscopic rectal cancer surgery and proposed an effective procedure for high ligation of the IMA. The latter technique was somewhat similar to ours; however, the neurofascial layer could not form a

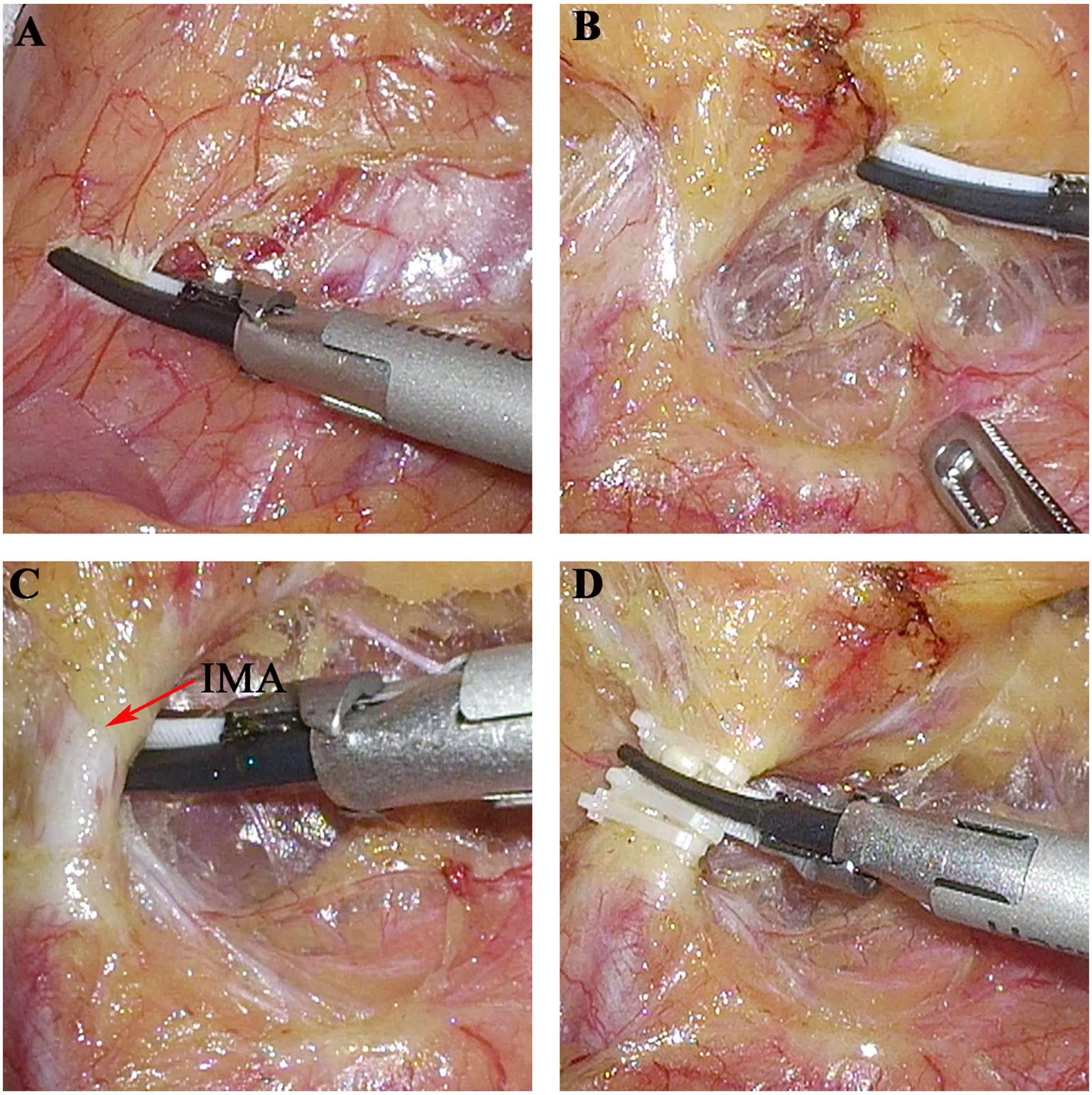


FIGURE 4 | The nerve-sparing technique of nerve plane-oriented. **(A)** The dissection extended up to the lower edge of the duodenum. **(B)** Extension from the superior hypogastric plexus nerve plane to the IMP nerve plane posterior to the IMA. **(C)** Abdominal aortic plexus nerve plane was gradually entered from cephalic to caudal by the "slope downhill" approach. **(D)** The IMA was ligated and cut above the IMP nerve plane. IMA, inferior mesenteric artery; IMP, inferior mesenteric plexus.

continuous plane in their surgical procedure, as shown in the current technique. Recently, Zheng et al. (29) reported that the left trunk of the IMP is a part of the IMA vascular sheath and proposed intrasheath separation of the IMA and left trunk for IMP preservation. In the present study, we believed that the IMP nerve plane could be separated from the IMA by enforcing traction and anti-traction. To maintain a balance between oncology and function, the nerve-sparing technique of nerve plane orientation was successfully performed in 68 patients without postoperative complications or urinary/sexual dysfunction. Therefore, this surgical technique is technically safe and feasible.

Moreover, the clear border of station 253 nodes remains vague and not standardized, and the area of station 253 nodes is regarded as an area containing the fat tissue around the IMA. Studies recommended that the left side is the inferior mesenteric vein (IMV), with the side dissection being the abdominal aorta, the cephalic side being the duodenum, and the caudal side being the IMA, which are the borders of station 253 nodes (30). In addition, most Chinese experts believe that the borders of station 253 nodes include the medial border as the area of the trunk between the point of origin of the IMA and the LCA, the lateral border as the medial margin of the IMV, the caudal border as the

TABLE 2 | Urinary and sexual function of participating patients.

Variable	No nerve plane-oriented group (N = 56)	Nerve plane-oriented group (N = 68)	*p*
IPSS, mean ± SD			
Preoperatively	4.3 ± 2.9	5.2 ± 2.5	0.062
6 months postoperatively	6.4 ± 4.7	6.0 ± 3.4	0.635
IIEF-5, mean ± SD			
Preoperatively	16.5 ± 3.4	17.7 ± 3.7	0.132
6 months postoperatively	13.9 ± 3.1	15.8 ± 3.7	0.015
FSFI, mean ± SD			
Preoperatively	29.2 ± 3.8	29.5 ± 3.7	0.638
6 months postoperatively	24.6 ± 4.6	27.7 ± 3.1	0.006
Urinary dysfunction, n (%)			
Preoperatively	5 (8.9%)	5 (7.3%)	0.748
6 months postoperatively	15 (26.8%)	8 (11.7%)	0.032
Sexual dysfunction, n (%)			
Preoperatively	7 (12.5%)	9 (13.2%)	0.903
6 months postoperatively	20 (35.7%)	13 (19.1%)	0.037

SD, standard deviation.
IPSS, International Prostate Symptom Score; IIEF-5, 5-item version of the International Index of Erectile Function; FSFI, Female Sexual Function Index.

point of origin of the LCA to its intersection with the IMV, and the cephalic border as the level of the root of the IMA (31). However, most studies have no clear definition of the dorsal border of station 253 nodes. In the present work, we believed that the IMP nerve plane is the dorsal border of station 253 nodes and should be preserved, which not only avoids damaging the IMP but also ensures station 253 node dissection in laparoscopic rectal cancer surgery.

Regarding urinary and sexual functions, in the present study, at 6 months after laparoscopic rectal cancer surgery, with the routine nerve-sparing technique, the rate of urinary dysfunction was increased by 17.9% (from 8.9% to 26.8%), while the sexual dysfunction rate was increased by 23.2% (from 12.5% to 35.7%). However, in the nerve-sparing technique of nerve plane orientation, the rate of urinary dysfunction was increased by 4.4% (from 7.3% to 11.7%), and the sexual dysfunction rate was increased by 5.9% (from 13.2% to 19.1%). Therefore, the nerve-sparing technique of nerve plane orientation confers faster recovery of urinary and urogenital functions.

In the present study, we regarded extra-nerve plane station 253 nodes as extra-mesenteric lymph nodes, which are unnecessarily cleaned, especially for patients with early rectal cancer. Extended station 253 node dissection not only provides no additional survival benefit but also increases the risk of nerve damage. However, some limitations should be acknowledged in this study, including the relatively small sample size and the lack of long-term follow-up for oncological outcomes. Therefore, further studies with large samples and long-term follow-up with oncological outcomes are required.

CONCLUSION

The presence of the nerve plane is helpful for IMP preservation. This nerve-sparing technique of nerve plane orientation is technically feasible and safe, which confers faster recovery of urinary and sexual functions.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Institutional Review Board of the Renmin Hospital of Wuhan University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

KL designed the study and prepared the manuscript draft. PP, HC, and JZ performed the data collection and analysis. QL and ST performed the H&E staining and immunohistochemical analysis. XH, FC, and YZ critically revised the manuscript for important intellectual content. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by grants from the Chenxiao-ping Foundation for the Development of Science and Technology of Hubei Province (CXPJJH121003-2103).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.853662/full#supplementary-material

REFERENCES

1. Japanese Society for Cancer of the Colon and Rectum. *General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum, and Anus. 6th ed*. Tokyo: Kanahara Shuppan (1998).
2. Lange MM, Buunen M, van de Velde CJ, Lange JF. Level of Arterial Ligation in Rectal Cancer Surgery: Low Tie Preferred Over High Tie. A Review. *Dis Colon Rectum* (2008) 51:1139–45. doi: 10.1007/s10350-008-9328-y
3. Sun Y, Chi P, Lin H, Lu X, Huang Y, Xu Z, et al. Inferior Mesenteric Artery Lymph Node Metastasis in Rectal Cancer Treated With Neoadjuvant Chemoradiotherapy: Incidence, Prediction and Prognostic Impact. *Eur J Surg Oncol (EJSO)* (2017) 43:85–91. doi: 10.1016/j.ejso.2016.09.005
4. Liang JT, Lai HS, Lee PH, Chang KJ. Laparoscopic Pelvic Autonomic Nerve-Preserving Surgery for Sigmoid Colon Cancer. *Ann Surg Oncol* (2008) 15:1609–16. doi: 10.1245/s10434-008-9861-x
5. Nano M, Dal Corso H, Ferronato M, Solej M, Hornung JP, Dei PM. Ligation of the Inferior Mesenteric Artery in the Surgery of Rectal Cancer: Anatomical Considerations. *Dig Surg* (2004) 21:123–6. doi: 10.1159/000077347
6. Li K, He X, Zheng Y. An Optimal Surgical Plane for Laparoscopic Functional Total Mesorectal Excision in Rectal Cancer. *J Gastrointest Surg* (2021) 25:2726–7. doi: 10.1007/s11605-021-05035-9
7. Li K, He X, Tong S, Zheng Y. Nerve Plane: An Optimal Surgical Plane for Laparoscopic Rectal Cancer Surgery? *Med Hypotheses* (2021) 154:110657. doi: 10.1016/j.mehy.2021.110657
8. Deng WH, Zheng YB, Tong SL, Cao FY, He XB, Xiao K, et al. Efficiency Analysis on Functional Protection of Nerve Plane-Oriented Laparoscopic Total Mesorectal Excision. *Zhonghua Wei Chang Wai Ke Za Zhi* (2019) 22:1144–51. doi: 10.3760/cma.j.issn.1671-0274.2019.12.009
9. Barry MJ, Fowler FJ, O'Leary MP, Bruskewitz RC, Holtgrewe HL, Mebust WK, et al. The American Urological Association Symptom Index for Benign Prostatic Hyperplasia. The Measurement Committee of the American Urological Association. *J Urol* (1992) 148:1549–57. doi: 10.1016/s0022-5347(17)36966-5
10. Kim HS, Kang JH, Yang SY, Kim NK. Long-Term Voiding and Sexual Function in Male Patients After Robotic Total Mesorectal Excision With Autonomic Nerve Preservation for Rectal Cancer: A Cross-Sectional Study. *Surg Laparosc Endosc Percutan Tech* (2020) 30:137–43. doi: 10.1097/SLE.0000000000000779
11. Rosen RC, Cappelleri JC, Smith MD, Lipsky J, Pena BM. Development and Evaluation of an Abridged, 5-Item Version of the International Index of Erectile Function (Iief-5) as a Diagnostic Tool for Erectile Dysfunction. *Int J Impot Res* (1999) 11:319–26. doi: 10.1038/sj.ijir.3900472
12. Wei B, Zheng Z, Fang J, Xiao J, Han F, Huang M, et al. Effect of Denonvilliers' Fascia Preservation Versus Resection During Laparoscopic Total Mesorectal Excision on Postoperative Urogenital Function of Male Rectal Cancer Patients: Initial Results of Chinese Puf-01 Randomized Clinical Trial. *Ann Surg* (2020) 274:e473–80. doi: 10.1097/SLA.0000000000004591
13. Rosen R, Brown C, Heiman J, Leiblum S, Meston C, Shabsigh R, et al. The Female Sexual Function Index (Fsfi): A Multidimensional Self-Report Instrument for the Assessment of Female Sexual Function. *J Sex Marital Ther* (2000) 26:191–208. doi: 10.1080/009262300278597
14. Wiegel M, Meston C, Rosen R. The Female Sexual Function Index (Fsfi): Cross-Validation and Development of Clinical Cutoff Scores. *J Sex Marital Ther* (2005) 31:1–20. doi: 10.1080/00926230590475206
15. Huh JW, Kim YJ, Kim HR. Distribution of Lymph Node Metastases Is an Independent Predictor of Survival for Sigmoid Colon and Rectal Cancer. *Ann Surg* (2012) 255:70–8. doi: 10.1097/SLA.0b013e31823785f6
16. Kang J, Hur H, Min BS, Kim NK, Lee KY. Prognostic Impact of Inferior Mesenteric Artery Lymph Node Metastasis in Colorectal Cancer. *Ann Surg Oncol* (2011) 18:704–10. doi: 10.1245/s10434-010-1291-x
17. Ubukata M, Itabashi M, Kameoka S. Japanese D3 Lymph Node Dissection in Low Rectal Cancer With Inferior Mesenteric Lymph Node Metastases. *World J Surg* (2014) 38:2724–9. doi: 10.1007/s00268-014-2617-9
18. Watanabe T, Muro K, Ajioka Y, Hashiguchi Y, Ito Y, Saito Y, et al. Japanese Society for Cancer of the Colon and Rectum (Jsccr) Guidelines 2016 for the Treatment of Colorectal Cancer. *Int J Clin Oncol* (2018) 23:1–34. doi: 10.1007/s10147-017-1101-6
19. Vogel JD, Eskicioglu C, Weiser MR, Feingold DL, Steele SR. The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Treatment of Colon Cancer. *Dis Colon Rectum* (2017) 60:999–1017. doi: 10.1097/DCR.0000000000000926
20. Kinugasa Y, Murakami G, Suzuki D, Sugihara K. Histological Identification of Fascial Structures Posterolateral to the Rectum. *Br J Surg* (2007) 94:620–6. doi: 10.1002/bjs.5540
21. Mike M, Kano N. Laparoscopic-Assisted Low Anterior Resection of the Rectum–A Review of the Fascial Composition in the Pelvic Space. *Int J Colorectal Dis* (2011) 26:405–14. doi: 10.1007/s00384-010-1107-2
22. Runkel N, Reiser H. Nerve-Oriented Mesorectal Excision (Nome): Autonomic Nerves as Landmarks for Laparoscopic Rectal Resection. *Int J Colorectal Dis* (2013) 28:1367–75. doi: 10.1007/s00384-013-1705-x
23. Zhou H, Ruan C, Sun Y, Zhang J, Wang Z, Hu Z. Nerve-Guided Laparoscopic Total Mesorectal Excision for Distal Rectal Cancer. *Ann Surg Oncol* (2015) 22:550–1. doi: 10.1245/s10434-014-4161-0
24. Liang JT, Lai HS, Lee PH. Laparoscopic Pelvic Autonomic Nerve-Preserving Surgery for Patients With Lower Rectal Cancer After Chemoradiation Therapy. *Ann Surg Oncol* (2007) 14:1285–7. doi: 10.1245/s10434-006-9052-6
25. Tejedor P, Sagias F, Celentano V, Khan JS. Nerve-Sparing Total Mesorectal Excision and Pelvic Neuroanatomy for Colorectal Surgeons. *Dis Colon Rectum* (2019) 62:1548–9. doi: 10.1097/DCR.0000000000001502
26. Li K, Chen D, Chen W, Liu Z, Jiang W, Liu X, et al. A Case-Control Study of Using Carbon Nanoparticles to Trace Decision-Making Lymph Nodes Around Inferior Mesenteric Artery in Rectal Cancer. *Surg Endosc* (2019) 33:904–10. doi: 10.1007/s00464-018-6384-9
27. Huscher CG, Rossetti A. Nerve-Sparing High Ligation of the Inferior Mesenteric Artery With Cavitron Ultrasonic Surgical Aspirator (Cusa). *Tech Coloproctol* (2017) 21:163. doi: 10.1007/s10151-016-1574-8
28. Sun Y, Zhang ZC, Zhou YD, Li P, Zeng QS, Zhang XP. High Ligation of the Inferior Mesenteric Artery With Nerve-Sparing in Laparoscopic Surgery for Advanced Colorectal Cancer. *Tech Coloproctol* (2021) 25:343–4. doi: 10.1007/s10151-020-02355-x
29. Zheng Z, Wang X, Huang Y, Lu X, Zhao X, Chi P. An Intrasheath Separation Technique for Nerve-Sparing High Ligation of the Inferior Mesenteric Artery in Colorectal Cancer Surgery. *Front Oncol* (2021) 11:694059. doi: 10.3389/fonc.2021.694059
30. Li K, Li Z, Yan B, Tan J, Chen D, Chen W, et al. Preoperative Carbon Nanoparticle Injection Improves Inferior Mesenteric Artery Lymph Node Retrieval in Patients With Rectal Cancer. *Surgery* (2021) 13:S0039–6060(21)00793-5. doi: 10.1016/j.surg.2021.08.023
31. Editorial Committee of Chinese Expert Consensus on Radical Resection of Rectal Cancer with Preservation of Left Colorectal Artery (2021 edition), Comprehensive Treatment Group of Colorectal Cancer, Anorectal Doctor Branch, Chinese Medical Doctor Association, Expert Committee on Prevention and Treatment of Rectal Cancer, Special Committee for General Surgery and Society of Integrated Traditional Chinese and Western Medicine. Chinese Expert Consensus on Radical Resection of Rectal Cancer With Preservation of Left Colonic Artery (2021 Edition). *Zhonghua Wei Chang Wai Ke Za Zhi* (2021) 24:950–5. doi: 10.3760/cma.j.cn441530-20210927-00389

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Advantages of publishing in Frontiers

OPEN ACCESS
Articles are free to read for greatest visibility and readership

FAST PUBLICATION
Around 90 days from submission to decision

HIGH QUALITY PEER-REVIEW
Rigorous, collaborative, and constructive peer-review

TRANSPARENT PEER-REVIEW
Editors and reviewers acknowledged by name on published articles

Frontiers
Avenue du Tribunal-Fédéral 34
1005 Lausanne | Switzerland

Visit us: www.frontiersin.org
Contact us: frontiersin.org/about/contact

REPRODUCIBILITY OF RESEARCH
Support open data and methods to enhance research reproducibility

DIGITAL PUBLISHING
Articles designed for optimal readership across devices

FOLLOW US
@frontiersin

IMPACT METRICS
Advanced article metrics track visibility across digital media

EXTENSIVE PROMOTION
Marketing and promotion of impactful research

LOOP RESEARCH NETWORK
Our network increases your article's readership