國立臺灣大學醫學院臨床醫學研究所

博士論文

Graduate Institute of Clinical Medicine
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Doctoral Dissertation

# 發展微創手術以治療需要多器官切除及重建之局部侵犯性大腸直腸癌

# Development of the Minimally Invasive Surgical Techniques for the Treatment of Locally Advanced Colorectal Cancer Requiring Multivisceral Resection and Reconstruction

廖御佐

Yu-Tso Liao

指導教授：梁金銅教授
黃凱文教授

Advisor: Jin-Tung Liang, M.D., Ph.D.
Kai-Wen Huang, M.D., Ph.D.

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# 口試委員會審定書

**PhD DISSERTATION ACCEPTANCE CERTIFICATE**
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（論文中文題目）(Chinese title of PhD dissertation)

發展微創手術以治療需要多器官切除及重建之局部侵犯性大腸直腸癌

（論文英文題目）(English title of PhD dissertation)

Development of the Minimally Invasive Surgical Techniques for the Treatment of Locally Advanced Colorectal Cancer Requiring Multi-visceral Resection and Reconstruction

本論文係廖御佐 D06421021 在國立臺灣大學醫學院臨床醫學研究所博士班完成之博士學位論文，於民國 111 年 12 月 30 日承下列考試委員審查通過及口試及格，特此證明。

The undersigned, appointed by the Institute of Clinical Medicine, National Taiwan University on 30th December, 2022 have examined a PhD dissertation entitled above presented by Yu-Tso, LIAO, D06421021 candidate and hereby certify that it is worthy of acceptance.

口試委員 Oral examination committee:

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台灣大學臨床醫學研究所



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# 中文摘要

**背景：**大腸直腸癌近年來已經成為高發生率及高盛行率的惡性腫瘤。使用腹腔鏡手術切除原發性腫瘤併淋巴結廓清已經是標準手術方式。然而外科醫學界對於以腹腔鏡手術治療局部侵犯性大腸直腸癌仍未有定論。所顧慮者在於：使用微創手術進行整塊多器官切除需要較高之技術難度，再者亦不清楚使用微創手術能否達到腫瘤學所要求之R0切除率並且得到令人滿意之手術成績，故目前標準治療方式仍以開腹手術為主。隨著近十年來腹腔鏡手術技術的之成熟及設備器材之發展，吾人猜想以微創手術治療局部侵犯性大腸直腸癌應為可行、安全及有效力之手術方式，值得回顧文獻評估並開發微創手術在此議題之適應症。另外機器人手術系統具有高解析度影像和多自由度的機器手腕可以達到細緻的體腔內縫合重建，近年來機器人各領域手術之發展呈現跳躍式進步，吾人亦猜測機器人手術之使用在局部侵犯性大腸直腸癌扮演愈來愈重要的角色。

**目的：**本研究旨在開發以微創手術治療需要多器官切除和重建之局部侵犯性大腸直腸癌之手術技巧，並且探討和更新微創手術在此議題之適應症，希望能夠提供日後以微創手術治療這類病人的實證以及指引未來研究方向。

**方法：**由前瞻性建置的資料庫中，吾人回溯性收集於 2006 年 6 月至 2020 年 11 月之間在臺大醫院、新竹分院及雲林分院三院區，接受腹腔鏡手術和機器人手術之局部侵犯性大腸直腸癌病人的臨床病理、術中後恢復以及腫瘤學資料。吾人將分析 cT4 局部侵犯性大腸直腸癌病人的術中後以及腫瘤學結果，並比較以微創手術來治療 cT4a 病人族群和 cT4b 需要多器官切除之大腸直腸病人癌族群的手術和腫瘤學結果。吾人將團隊成果和文獻結果進行比較分析，試圖釐清何種遭 cT4b 局部



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侵犯之器官，能夠藉由微創手術方式進行整塊多器官切除手術中獲得最好治療成果。其次，吾人聚焦於局部侵犯性大腸直腸癌合併膀胱侵犯的族群。由前部分結果得知膀胱為最容易遭到 cT4 大腸直腸癌侵犯之器官；重建被部分切除之膀胱需要較高之腹腔鏡手術技巧。吾人將探討以腹腔鏡手術和機器人手術兩種微創手術之手術中後和腫瘤學成績，嘗試開發機器人手術在此議題的應用性。最後，吾人希望建立起局部侵犯性大腸直腸癌的手術策略指引，提供臨床實證力基礎。本研究使用敘述統計、推論統計和 Cox 比例風險模型進行統計學分析。

**結果**：本研究共收入 128 位 cT4 局部侵犯性大腸直腸癌病人；進食時間中位數為 6 天，術後住院天數中位數為 11 天，開腹轉換率為 7.8%，併發症率為 27.3%，三十天死亡率為 0.78%；對於 90 位 cT4M0 病人的 R0 切除率為 92.2%。這些結果達到與文獻相當之手術成績。進一步比較 cT4a 和需要多器官切除 cT4b 大腸直腸癌，發現後者手術時間、失血量、進食時間和住院天數較長，但併發症和 R0 切除率無統計顯著差異。本研究受侵犯切除之器官包括膀胱、腹壁/腹膜、子宮附件(和卵巢)及小腸等；上述器官以微創手術方式進行整塊多器官切除和重建是安全而且可行的。本研究亦收納 41 位侵犯到膀胱之局部侵犯性大腸直腸癌病人進行分析，當中 32 位接受腹腔鏡手術，9 位接受機器人手術。兩組病人在手術中後結果及存活率上無統計顯著差異。R1 切除率是降低無病存活率的唯一獨立預後因子。

**結論**：以腹腔鏡手術治療局部侵犯性大腸直腸癌是安全而且可行的方式，包括需要多器官切除及重建之局部侵犯性大腸直腸癌。膀胱是局部侵犯性大腸直腸癌最常侵犯的器官之一，以機器人手術方式來切除侵犯性大腸直腸癌以及受侵犯之膀胱是可行的手術方式，而且能夠達到和腹腔鏡手術相似的手術成績。本研究也指出：為了克服現階段文獻之選擇性偏差，高證據力之臨床隨機分派研究以探討微



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創手術治療需要多器官切除及重建之局部侵犯性大腸直腸癌是迫切需要的。另外欲探討微創手術在局部侵犯性大腸直腸癌的角色，以受侵犯器官為區分導向之研究將更能釐清微創手術在真實世界的手術和腫瘤學效益。

**關鍵字**：微創手術、腹腔鏡手術、機器人手術、局部侵犯性大腸直腸癌、cT4 大腸直腸癌、cT4b 大腸直腸癌、併發症、預後



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# ABSTRACT

**Background:** The incidence and prevalence of colorectal cancer (CRC) have recently increased worldwide. Laparoscopic colectomy combined with radical lymph node dissection has become the standard surgical method for CRC treatment. However, its application for treating of locally advanced CRC (LACRC) remains controversial. The main concerns surround the high technical demands of minimally invasive surgery for en bloc multivisceral resection, which may lead to inadequate R0 resection and increased surgical complications. Therefore, open surgery remains the standard treatment for LACRC. Owing to the maturation of laparoscopic techniques among surgeons and the development of surgical and optical equipment in the last two decades, we hypothesized that laparoscopic surgery is a safe, feasible, and efficacious method for treating LACRC; therefore, the indication for minimally invasive surgery is broadened. On the other hand, a robotic surgical system equipped with high-resolution imaging systems and high-freedom robotic wrists allows intracorporeal reconstruction, which facilitates robotic surgery to a giant leap. We also hypothesized that robotic surgery plays an increasingly important role in the treatment of LACRC.

**Methods:** A prospectively maintained database of patients who underwent laparoscopic or robotic surgery at the National Taiwan University Hospital, Hsinchu Branch, and Yunlin Branch was retrospectively reviewed from June 2006 to November 2020. Clinicopathological, intraoperative, postoperative and oncologic results of these patients were collected. Then, patients with LACRC were classified into the cT4a and cT4b groups requiring multivisceral resection. Surgical and oncologic outcomes were compared between the cT4a and cT4b groups. A literature review will be conducted, and the results will be compared with those of our study. We aimed to identify which organs



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invaded by cT4b LACRC can achieve the best surgical outcomes using laparoscopic en bloc multivisceral resection. In our previous study, the urinary bladder was the organ most vulnerable to invasion by cT4b LACRC, which requires high surgical skills for reconstruction after partial cystectomy. This study focused on a specific patient group with cT4b LACRC and urinary bladder invasion. Robotic surgery was performed in patients with cT4b LACRC who required multivisceral resection. The surgical and oncologic results of robotic and laparoscopic surgeries were compared between the two surgical methods. Finally, we established guidelines for the surgical planning of LACRC, which may serve as a basis for future studies. Descriptive statistics, inferential statistics, and Cox proportional hazard models were used.

**Results:** We recruited 128 cT4 LACRC patients undergoing MIS. The open conversion was 7.8%. The complication rate, defined as Clavien–Dindo classification ≥ II, was 27.3%, and the postoperative 30-day mortality was 0.78%. R0 resection rate was 92.2% for 90 cT4M0 patients. The median time to soft diet was 6 days, and the median postoperative length of stay was 11 days. These surgical results are comparable with those reported in previous studies. Further subgroup analysis showed cT4b LACRC patients requiring multivisceral resection demonstrated a longer operative time, increased blood loss, prolonged time to resume a soft diet and postoperative length of stay than those of cT4a LACRC patients. However, no significant difference between the two groups was found in terms of complications and R0 rates. The resected organs in this study included the urinary bladder, abdominal wall/peritoneum, adnexa, and small bowel, which can be safely and feasibly performed laparoscopically. Furthermore, we recruited 41 patients with LACRC patients invading the urinary bladder. Among them, laparoscopic surgery was performed in 31 patients, whereas robotic surgery in nine patients. There was no statistical difference in terms of surgical and oncologic outcomes between two groups.



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R1 resection was detected as the only independent prognostic factors for reduced disease-free survival (hazard ratio 21.386; 95% confidence interval 1.991–229.723; p = 0.0115).

**Conclusions:** The present dissertation indicates that laparoscopic surgery is safe and feasible for treating LACRC, including cT4 LACRC which requires multivisceral resection and reconstruction in selected patients. It has been shown that the urinary bladder is the organ most frequently invaded by LACRC. The robotic surgery can be performed safely for treating LACRC invading the urinary bladder, with similar surgical results to laparoscopic surgery. However, further prospective, randomized controlled trials are mandatory to reach high-level evidence to clarify the role of minimally invasive surgery for cT4b LACRC. Moreover, further organ-oriented studies will provide better convincing functional and oncologic data regarding the role of minimally invasive surgery in multivisceral resection for treating cT4b LACRC in the real world.

**Keywords:** minimally invasive surgery, laparoscopic surgery, robotic surgery, locally advanced colorectal cancer, cT4 colorectal cancer, T4b colorectal cancer, complication, outcome



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# ABBREVIATIONS

| | |
|---|---|
| **AJCC** | American Joint Committee on Cancer |
| **ASA** | American society of Anesthesiology |
| **CI** | Confidence interval |
| **CRC** | Colorectal cancer |
| **CT** | Computed tomography |
| **cT4** | Clinically T4 |
| **DFS** | Disease-free survival |
| **ERAS** | Enhanced recovery after surgery |
| **LACRC** | Locally advanced colorectal cancer |
| **MIS** | Minimally invasive surgery |
| **MRI** | Magnetic resonance imaging |
| **NCCN** | National Comprehensive Cancer Network |
| **nCRT** | Neoadjuvant chemoradiation therapy |
| **OS** | Overall survival |
| **PET** | Positron emission tomography |
| **pT4** | Pathologically T4 |
| **TNM** | Tumor–node–metastasis |



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# Chapter 1 Introduction

## 1.1 Current status of laparoscopic surgery for CRC

In 1983, a German surgeon, Semm, performed the first laparoscopic appendectomy using gynecology and obstetrics instruments.[1] The success of the first laparoscopic surgery led to the development of a new era of minimally invasive surgery (MIS). Thereafter, endoscopic or laparoscopic surgery has gradually been introduced in most surgical specialties and has revolutionized conventional open surgery, including esophageal, gastric, hepatobiliary, colorectal, gynecologic, urologic surgery, and some extraperitoneal organs such as the breast, thyroid, and hernia surgery. MIS has brought about tremendous advancements in improving patients' short- and long-term outcomes and is the standard procedure in many kinds of abdominal surgery, including colorectal surgery.

MIS is characterized by its use of advanced optical systems and surgical instruments to perform operation utilizing smaller abdominal incisions, resulting in better recovery compared to conventional open surgery. Owing to these advantages, MIS has gained acceptance gradually in many surgical fields, including colorectal cancer (CRC) treatment. So far, high-level evidence has proven that laparoscopic surgery offers the benefits of faster postoperative recovery without negatively affecting oncologic outcomes. Therefore, laparoscopic surgery has become the mainstay treatment for CRC.[2-4]

Conventionally, open abdominal surgery is the standard approach for treating colorectal diseases like diverticular diseases and CRC. However, the introduction of MIS has revolutionized conventional open surgery. The advantages of MIS depend on the advancement of equipment such as the optical system and steady $CO_2$ inflation system,



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innovation of the endoscopic/laparoscopic surgical instruments, and the enthusiastic devotion of surgical forerunners who continue to improve the surgical skills in laparoscopic surgery, which allows laparoscopic surgery to be safe, feasible, and efficacious in abdominal surgery. There are two examples of improvements in surgical skills. The first concerns surgical procedures. In the procedure of low anterior resection, the sigmoid and rectum are traditionally mobilized from the white line of Toldt to the mesocolon, that is, the lateral-to-medial approach; however, the medial-to-lateral approach is much more efficient in mobilizing the sigmoid colon and rectum during laparoscopic surgery because of the light direction of the endoscope.[5] Moreover, the magnification and high-resolution of the endoscope enable detailed visualization of the anatomical structure and meticulous dissection in the narrow cavity during total mesorectal excision (TME). Second, the innovation and introduction of autosuture instruments, e.g., endoGIA, allowed bowel transection and anastomosis in a laparoscopic approach, future making the colorectal anastomosis (e.g., double-stapling approach) in the pelvic cavity efficacious and efficient.

With the above-mentioned advancements in equipment and technical skills, accumulating data supports the clinical value of laparoscopic surgery. Several early and later large randomized controlled studies, such as MRC CLASICC, COLOR, COST, ALCCaS, ACOSOG Z6051, and Barcelona trials, confirmed that laparoscopic surgery harbors the benefits of less postoperative pain, quicker bowel restoration, shortened length of stay, and fewer complications such as wound infection, adhesive ileus, and ventral hernia with oncologic outcomes similar with those of open surgery in terms of radicality, lymph node retrieval, disease-free survival, and overall survival.[4,6-10] Several systemic reviews and meta-analyses have validated the superiority of laparoscopic surgery over open surgery for colorectal patients who undergo laparoscopic surgery in



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that laparoscopic surgery demonstrates better clinical results without compromising oncologic outcomes when compared with those of open surgery.[11,12] The current guidelines of large surgical societies in the United States and Europe recommend the laparoscopic method as the standard treatment for colon cancer.

Guidelines from the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) and American Society of Colon and Rectal Surgeons (ASCRS) state:

"*A minimally invasive surgical approach should be used whenever the expertise is available and appropriate. Grade of recommendation: strong recommendation based on high-quality evidence, 1A.*"[13] According to the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system, the grade IA denotes the implementation of MIS is strongly recommended and can be introduced without reservation to most patients in most situations (Table 1).

Furthermore, guidelines for Perioperative Care in Elective Colorectal Surgery proposed by the Enhanced Recovery After Surgery (ERAS) Society in 2018 strongly recommends MIS over open surgery.

"*A minimally invasive approach to colon and rectal cancer has clear advantages for improved and more rapid recovery, reduced general complications, reduced wound-related complications including incisional hernia and fewer adhesions. It is also an enabler for successful administration of many of the major components of ERAS such as opiate sparing analgesia and optimized fluid therapy.*"[14]

In the most updated version of National Comprehensive Cancer Network (NCCN) guidelines advocated (version 2. 2022) that experienced surgeons should perform minimally invasive surgery to achieve better postoperative outcomes.



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"*The surgeon has experience performing the laparoscopically assisted colorectal operation.*" (NCCN Guidelines Version 3.2022 Colon Cancer)[15]

"*The surgeon should have experience performing minimally invasive proctectomy with TME.*" (NCCN Guidelines Version 3.2022 Rectal Cancer)[16]

In conclusion, the clinical value of laparoscopic surgery has been confirmed in terms of surgical and oncologic outcomes for treating early CRC.[9] Current guidelines recommend laparoscopic surgery as the gold standard for treating CRC since its first induction in 2004.[17]

## 1.2 Robotic surgery: a new surgical modality for CRC

The SAGES defined robotic surgery as " a surgical procedure or technology that adds a computer technology-enhanced device to the interaction between a surgeon and a patient during a surgical operation".[18] In robotic surgery, surgeons can remotely perform robotic surgery using specific robotic surgical systems. The robotic surgical system is equipped with robotic arms and wrists with high degrees of freedom, allowing surgeons to perform complex surgical tasks, such as intracorporeal suturing and knotting. Moreover, the robotic surgical system harbors a camera with high-resolution three-dimensional vision and magnification. Further, the camera was fixed to a robotic arm, allowing stable operative vision. A surgeon can control the camera discretionarily. Therefore, the advantages of improved surgical vision, dexterity, and surgeon ergonomics overcome the limitations of laparoscopic surgery, including 2D vision and poor ergonomics due to long and rigid instruments.



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The United States Food and Drug Administration approved the usage of the Da Vinci Robotic system in 2000.[19] Robotic surgical systems currently on the market include Puma 560, PROBOT, ROBODOC, Senhance (Senhance, TransEnterix Surgical Inc.), and Da Vinci Robotic surgical system (Da VinCi, Intuitive Surgical Inc.). Among these, the Da Vinci Robotic system has the highest market share in the field of abdominal surgery.

Initially, the adoption of robotic surgery was driven by urologists and gynecologists and then spread to other abdominal surgeries, including colorectal surgery. Robotic surgery is widely used to treat CRC. Emerging studies have shown that robotic surgery reproduces quick recovery and favorable oncologic outcomes compared to laparoscopic surgery.[20,21] Additionally, the enhanced maneuverability of robotic wrists has allowed surgeons to perform multivisceral resection and reconstruction simultaneously,[22-24] though clinical data are limited in the literature.

## 1.3 Unmet need for MIS for the treatment of CRC

### 1.3.1 Opinion about laparoscopic surgery for LACRC in current guidelines

Laparoscopic surgery has become the mainstay method for treating CRC since its initial introduction in 2004.[9] However, laparoscopic surgery remains a relative contraindication for T4 stage LACRC, even though its efficacy in early CRC is well recognized.

LACRC accounts for approximately 15-20% of patients with CRC.[25,26] Further, 10–20% of patients with LACRC are considered to require multivisceral resection at the time of initial diagnosis.[27] LACRC, usually denoted T3-4 or positive N-staging, is similar to those defined as locally advanced cancer in breast cancer or pancreatic cancer.[28] Here,



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we adopted the definition of LACRC in which locally advanced colon cancer was defined as cT4 and/or pT4 stage.[29,30]

If cancer invades adjacent organs or structures, i.e., T4b cancer according to the American Joint Committee on Cancer (AJCC 8$^{th}$), multivisceral en bloc resection is required. The goal of the surgery is complete extirpation of the cancer with clear margins (R0 resection). An appropriate R0 rate is the most important prognostic factor that may decrease the local recurrence and prolong long-term overall survival.[31,32] Open surgery showed a wide range of R1 rates for LACRC required multivisceral resection between 2.2 and 62.5%.[33] In early randomized clinical trials, including the Barcelona, COST, COLOR, and ALCCaS trials, locally advanced colon cancer was excluded.[4,6,9] In the MRC CLASICC and ACOSOG Z6051 trial, only a small portion of pT4 LACRC or locally advanced rectal cancer was enrolled.[7,34] Given the suboptimal R0 rate and technical complexities for multivisceral organ resection and reconstruction in laparoscopic surgery, open surgery is conventionally deemed as the preferred surgical method to ensure en bloc resection.

According to the guidelines of the SAGES in 2013, a laparoscopic approach for LACRC is not recommended.

"*For locally advanced adherent colon and rectal tumors, an en bloc resection is recommended. We suggest an open approach if laparoscopic en bloc resection* ***cannot*** *be adequately performed. (Quality: low; weak)"*.[35]

Similar recommendations were made by the Japanese Society for Cancer of the Colons and Rectums in 2018. The guidelines state the following.

"*The indications for laparoscopic surgery are determined by considering the* ***surgeon's experience skills****, as well as tumor factors, such as the location and degree of progression*



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*of the cancer, and patient factors, such as obesity and history of open abdominal surgery*".[36]

To date, the NCCN guidelines remain conservative regarding the application of MIS for the treatment of LACRC.

"*Minimally invasive approaches are generally not indicated for locally advanced cancer or acute bowel obstruction or perforation from cancer.*" [37]

According to these guidelines, LACRC may be performed by surgeons experienced in MIS in selected patients, although the criteria are not clearly defined in the current guidelines. MIS is generally considered a contraindication for the treatment of locally advanced colon cancer.

### 1.3.2 Updated reviews of laparoscopic surgery for LACRC

With the accumulated clinical experience in laparoscopic surgery, attempts to use laparoscopic surgery have been initiated. Some retrospective studies have reported the results of laparoscopic surgery for treating LACRC.

A literature review of previous studies in PubMed using the keywords "minimally invasive surgery", "laparoscopic surgery", "cT4 colorectal cancer", "pT4 colorectal cancer", "locally advanced CRC" or "multivisceral resection". The results are presented in Table 2. Reviewing these studies, we found that surgeons with experience in laparoscopic surgery can safely and feasibly treat selected patients with LACRC. The preliminary results regarding oncologic outcomes, including the R0 rate and overall survival, are acceptable.[33,38-60]

A recent meta-analysis conducted by Podda *et al*. included 24 observational studies over 9 years, showing that compared with open surgery, laparoscopic surgery is



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related to better clinical outcomes and exhibits oncologic safety for the treatment of selected patients with LACRC.[61] Similar conclusions were drawn from other meta-analyses conducted by Liu *et al.* and Feinberg *et al*.[30,62]

### 1.3.3 Unsolved problems of laparoscopic surgery for the treatment of LACRC

Several important issues should be addressed and clarified based on previous studies. First, T4 LACRC comprises T4a and T4b lesions and represents different surgical strategies. T4a LACRC did not penetrate the visceral peritoneum. Therefore, the principles and procedures of surgery are the same as those for the resection of T3 cancer. Colectomy with an adequate resection margin and radical lymph node dissection, indicated by the extension of the primary tumors, is sufficient. However, T4b LACRC that invades adjacent organs requires multivisceral resection. The surgical procedures are relatively complex. We found heterogeneity in T4 LACRC inclusion criteria in previous studies. Most studies included the inequality or disproportion of T4a and T4b LACRC between the laparoscopic and open groups. The inequality or disproportion of T4a and T4b LACRC between the two surgical methods may significantly influence the outcomes of comparative studies. Selection bias severely hinders the conclusions drawn from previous studies.

Second, the structures or organs invaded by the T4b LACRC were different. Some organs that adhere to the cancer are the parietal peritoneum, peri-renal structure (e.g., Gerota's fascia or peri-renal fat), and female adnexa, for which concomitant en bloc resection is sufficient. Some organs invaded by the tumor include the urinary bladder, small bowel, and vagina, for which synchronous repair and reconstruction are required



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and, thus, become technically challenging. To evaluate the safety, feasibility, efficacy, and oncologic benefits of MIS, the structures and organs invaded by LACRC should be considered.

Third, most previous studies included patients with pathological T4 (pT4) LACRC to evaluate the outcomes of laparoscopic surgery; however, surgeons are more likely to encounter patients with clinical T4 (cT4) LACRC in clinical practice. Any suspicious cancerous involvement should be removed to achieve R0 resection. This procedure may inevitably resect organs or structures that are pathologically uninvolved in cancer. This procedure increases the potential risks. Therefore, in cT4 LACRC, surgeons may face challenges in determining the extent of resection. Surgeons should balance surgical risks and benefits of cancer clearance. Therefore, studies on patients with cT4 LACRC undergoing MIS would truly reflect real-world conditions. However, studies that recruited patients with cT4b LACRC are limited.[38,63]



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# Chapter 2 Objectives

## 2.1 Research questions and clinical significance

With regard to the current status and unmet need for MIS for the treatment of LACRC, the research questions guiding the work that informed the dissertation are as follows:

1. What are the clinicopathological features of patients with LACRC who undergo MIS?
2. What clinicopathological features of patients with LACRC can benefit from MIS?
3. Is MIS a safe and feasible procedure for treating patients with LACRC?
4. Are the short-term surgical outcomes of MIS equivalent to those of open surgery for treating patients with LACRC?
5. Do the oncologic outcomes of MIS justify its application compared with those of open surgery in patients with LACRC?
6. What is the safety, feasibility, and efficacy of robotic surgery for the treatment of LACRC?

The clinical significance of these questions is as follows.

1. We will draw a clinical picture of patients with LACRC undergoing MIS in terms of clinicopathological data and surgical outcomes. Related data were limited to Taiwan.
2. We will explore the criteria for resectability of LACRC that require multivisceral resection and reconstruction. These results defined the indications for MIS in these patient groups.



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3. This study aimed to evaluate the safety and feasibility of MIS in patients with LACRC.
4. Our study evaluated and compared the short-term surgical outcomes of MIS in our study with those reported about open surgery in previous studies.
5. Our study compared the long-term oncologic outcomes of MIS with those of open surgery in previous studies.
6. This study aimed to explore the potential applications of robotic surgery for complex diseases, including LACRC.

## 2.2 Hypothesis and study aims

Laparoscopic surgery for treating CRC was introduced in the late 20s and has gained wide acceptance within the last two decades based on accumulating clinical evidence. However, the recommendation remains conservative pertaining to the application of MIS for treating LACRC in the guidelines proposed by large surgical societies and the NCCN guidelines. We found that these recommendations lacked support from clinical evidence and were based only on expert opinions. The application of MIS should be investigated along with the development of surgical technology and skills.

The hypotheses of this study were as follows:

1. We hypothesized that MIS could be safely performed with LACRC with comparable short-term surgical and long-term oncologic outcomes with those of open surgery in selected patients.
2. Robotic surgery can be incorporated into the surgical armamentarium to treat LACRC.



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In the context of current evidence, the unmet need in the literature, and the hypotheses of our study, the study aims are described with the following objectives:

1. To evaluate the safety, feasibility, and efficacy of MIS in treating locally advanced colon cancer.
2. We evaluated the clinical benefits of MIS for treating LACRC.
3. To justify the short-term surgical and long-term oncologic outcomes of MIS for the treatment of LACRC.
4. We evaluated the safety, feasibility, and efficacy of robotic surgery for the treatment of LACRC.
5. Identifying the characteristics of patients with LACRC who are potential candidates for MIS.
6. Our data can serve as a foundation for constructing high-level randomized controlled studies and meta-analyses.

As surgeons, we believe that the enthusiasm of surgeon precursors is constantly pushing the boundary of applying surgical technology in complicated scenarios, such as LACRC requiring multivisceral resection and reconstruction. Given the huge development in laparoscopic instruments and maturation in surgical skills, we believe that it is time to evaluate the outcomes of MIS for the treatment of LACRC requiring multivisceral resection and reconstruction. Our ultimate goals were to justify the current role of MIS and to inspire future high-level studies on the treatment of LACRC.



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# Chapter 3 Material and methods

Since the introduction of laparoscopic surgery at the National Taiwan University Hospital (NTUH) in 2005, we have accumulated significant clinical experience in MIS. Our surgical team has reported surgical techniques for minimally invasive multivisceral resection of LACRC, which was proven safe and feasible in selected patients.[64-67] Additionally, we have developed surgical techniques for single-incision laparoscopic surgery to treat complicated emergency appendicitis.[68,69] We also intended to improve postoperative care. For example, our study demonstrated the unnecessity of routine abdominal drainage following laparoscopic appendectomy for treating complicated appendicitis.[70] Putting our previous work, we demonstrated mature surgical skills in MIS and improved postoperative care protocols in our surgical team. Additionally, a sufficient number of patients with LACRC at our institute could help to answer the research questions in this study.

## 3.1 Study cohort

### 3.1.1 Cohort one: the cT4 LACRC

We recruited patients with cT4 LACRC undergoing laparoscopic surgery and robotic surgery at the NTUH, Yunlin Branch, and Hsinchu Branch from September 2006 to March 2019. Patient data were obtained from the prospectively constructed database of the National Taiwan University. The last follow-up date was on December 1, 2019.

Patients recruited in this study were either preoperatively staged as cT4 LACRC according to computed tomography (CT), magnetic resonance imaging (MRI), whole-



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body bone scan, and/or positron emission tomography (PET), or intraoperatively staged as cT4 LACRC by the operative findings including tumor involvement of visceral peritoneum or tumor tethering to the nearby structure. We recruited patients with cT4 LACRC regardless of nodal status.

The 8th edition of AJCC staging system define cT4 LACRC as follows: (1) the visceral peritoneum was penetrated by the tumors (cT4a); (2) the adjacent organ was directed invaded by the tumors (cT4b). Accordingly, cT4 LACRC in this study included the following conditions: (1) cT4a LACRC without distant metastasis or peritoneal seeding (cT4aM0); (2) cT4b LACRC with adjacent organ involvement but no distant metastasis or peritoneal seeding (cT4bM0); and (3) cT4 LACRC with distant metastasis or peritoneal seeding and/or resectable/unresectable distant metastasis, such as in the liver or lungs (cT4M1).

Dr. Yu-Tso Liao performed six laparoscopic surgeries, while Professor Jin-Tung Liang performed the other 122 surgeries including laparoscopic and robotic surgery.

### 3.1.2 Cohort two: the cT4b LACRC invading the urinary bladder

Information on patients' clinicopathology, surgical and oncologic outcomes were obtained retrospectively from the prospectively maintained database of consecutive patients with cT4b LACRC invading the urinary bladder undergoing either laparoscopic or robotic surgery at the NTUH and two of its branch hospitals (Hsinchu and Yunlin branch). The laparoscopic surgery was performed between June 2006 and August 2020); while the robotic surgery was performed between November 2013 and November 2020. The laparoscopic surgery was performed by two surgeons (Professor Jin-Tung Liang and



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Dr. Yu-Tso Liao), whereas robotic surgery was performed by one surgeon (Professor Jin-Tung Liang). Before performing multivisceral resection, two surgeons had experiences of more than 200 laparoscopic colectomy procedures. Moreover, both laparoscopic and robotic surgeries were routinely performed at our institute.

The laparoscopic method was performed between June 2006 and August 2020 to treat patients with LACRC invading the urinary bladder, whereas the robotic method was used between November 2013 and November 2020.

The inclusion criteria in cohort two were listed as followed: (1) LACRC invading the urinary bladder; (2) elective and curative-intent surgery; and (3) the American Society of Anesthesiology (ASA) class ≤ III. The exclusion criteria were listed as followed: (1) cT4b LACRC invading organs other than the urinary bladder; (2) emergency surgery; (3) previous history of abdominal surgery for colorectum, or other pelvic organs; and (4) body mass index (BMI) >35 $kg/m^2$.

## 3.2 Definition of the terms

### 3.2.1 Surgical outcomes

#### 3.2.2.1 Operative time

Operative time indicated the time between the skin incision and the wound dressing application.



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3.2.2.2 Postoperative length of stay

The postoperative length of stay was evaluated according to the duration between the time that patient left the recovery room and the time of discharge.

3.2.2.3 Time to resume a soft diet

The time to resume a soft diet was evaluated according to the duration between the time that patient left the recovery room and the time that patient first resumed the soft diet.

3.2.2.4 Complication

We use the Clavien–Dindo classification system to evaluate the severity of surgical complications. Surgical complications were recorded within 30 days of the surgery. Complications evaluated in this study contained surgical site infection, postoperative ileus, and IAA formation. Surgical site infection was defined as gross pus formation or erythematous presentation in the wound that required antibiotic treatment. Postoperative ileus included presentation of nausea, vomiting, or abdominal fullness, which was confirmed by plain abdominal radiography or abdominopelvic CT. IAA formation indicated the abdominal abscess formation presented on ultrasound or CT.



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3.2.2.5 Radicality

R0 resection was determined by microscopic examination and defined as negative involvement of the specimen margin. R1 resection was defined as positive involvement of the specimen margin on microscopic examination or microscopic involvement of < 1 mm from the resected margin. R2 resection indicated grossly positive resection margins.

## 3.2.5 Curative intent and palliative surgery

Surgery for cM1 lesions was defined as a palliative treatment. A curative-intent surgery was performed if surgeons attempted to achieve R0 resection of the primary tumor in patients with cM0 disease. In this study, curative-intent surgery was performed in all cM0 patients.

## 3.2.6 Local recurrence and distant metastasis

We defined local recurrence as suspicious cancerous lesions presented in previous operative site on imaging studies such as CT, MRI, or PET. We defined distant metastasis as any lesion of suspicious cancerous involvement away from the structure previously invaded by the primary CRC.

## 3.2.7 Disease-free survival and overall survival

We defined the disease-free survival (DFS) as the duration between surgery and local recurrence or distant metastasis. We defined the overall survival (OS) as the duration



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between surgery and death. We calculated the 5-year DFS and OS rates after excluding patients with pM1 CRC.

## 3.3 Surgical techniques

MIS includes laparoscopic and robotic surgery. At the NTUH, laparoscopic surgery has been the mainstay approach for treating colorectal diseases since 1995, and robotic surgery has been introduced since 2011. Currently, both laparoscopic and robotic surgeries are routinely performed during NTUH.

Two surgeons (Professor Jin-Tung Liang and Dr. Yu-Tso Liao) performed laparoscopic surgery. Professor Liang has more than two decades of experience in laparoscopic surgery, whereas Dr. Laio has performed laparoscopic surgery since 2011. Both surgeons had accumulated experience with > 200 cases of laparoscopic surgery for CRC before performing multivisceral resection. Professor Liang performed all the robotic surgeries. Professor Liang started performing robotic surgery in 2011 and had robotic certification in the same year.

### 3.3.1 Laparoscopic surgery

The procedures for laparoscopic surgery for CRC have been detailed in our previous studies[71,72] In brief, after completion of the patient position, port setting, and pneumoperitoneum, the entire abdomen was first inspected laparoscopically. The organs invaded by the tumor were then evaluated to determine the extent of the simultaneous multivisceral resection. The procedure chosen for the resection of the primary CRC was in accordance with the location of the tumor, the territory of the feeding vessels, and organ



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invasion. The procedure of multivisceral resection dissection followed en bloc resection of the primary CRC and the organs that had invaded. Clear resection margins, including the radical and circumferential margins, were attempted. Reconstruction of the resected organ depends on its extent and location. The reconstruction of the urinary bladder described in Chapter 5 is detailed in Section 3.2.3.

### 3.3.2 Robotic surgery

All robotic operations were performed utilizing the Da VinCi® surgical system Si or Xi (Intuitive Inc., Sunnyvale, CA, USA). The procedure was initiated by inspection of the entire abdomen. Primary CRC and organ invasion were evaluated to determine the extent of the resection. Robotic surgery was performed on the left colorectum. The procedure is as follows. The anatomical relationship between primary tumor and invaded site of the urinary bladder were evaluated. Dissection commenced as previously standardized procedures, namely, a medial-to-lateral approach of the left colon, ligation of the inferior mesenteric vessels, and complete mobilization and takedown of the splenic flexure. The left colon was mobilized until the region of the urinary bladder invaded by primary CRC was noticed. The procedures of resection and reconstruction for the urinary bladder were described in the next section. Bowel continuity was reconstructed using the double-stapling technique after removing all the specimens.



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### 3.3.3 Resection and reconstruction of the urinary bladder

All procedures were performed with the curative-intent surgery. The bladder wall was incised, and the extent of resection was carefully decided during the operation to maintain a safety margin. The primary tumor and invaded wall of urinary bladder was extirpated en bloc. Throughout the procedure, the trigone of the urinary bladder was carefully inspected and examined.

In patients undergoing laparoscopic surgery, we used the 1-0 absorbable Vircyl® sutures or barbed V-Loc® sutures (Covidien, Inc., Mansfield, MA) to repair the defect of urinary bladder by a continuous, two-layer fashion. In patients undergoing robotic surgery, we used the 1-0 absorbable Vircyl® suture (polyglactin 910) to repair the urinary bladder defect with a continuous, two-layer fashion. After the retrograde cystography confirmed the complete healing of the urinary bladder, the urinary catheter was removed.

## 3.4 Preoperative preparation and Postoperative and Surveillance

### 3.4.1 Preoperative preparation

All patients in this study were diagnosed with CRC based on preoperative colonoscopy findings and pathological examination of the biopsied specimens. These patients were evaluated included medical history, physical examination of the body, rectal examination, blood test and imaging studies. The blood tests included complete blood cell count, differential count of the white blood cell, electrolytes, liver and renal function, coagulation factors, and carcinoembryonic antigen (CEA) levels. All patients underwent



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routine chest radiography and CT of the chest, abdomen, and pelvis. Whole-body MRI, whole-body bone scan, or PET were performed to fully stage the extent of the tumor in selected patients if necessary. The patients' treatment plans, including the administration of neoadjuvant chemoradiation therapy and/or other multimodal interventions, were discussed in a permanent multidisciplinary team at NTUH and its two branches. After surgery, the definite diagnosis and staging of the CRC were confirmed by pathologists.

All clinicopathologic features and surgical outcomes were registered to a prospectively maintained database. The clinicopathologic data included age, gender, BMI, past history of underlying disease, ASA class, and tumor–node–metastasis (TNM) staging. Surgical outcomes included operative time, blood loss, intraoperative event, number of lymph nodes harvested, the radicality of the resected margins and circumferential resection margin (CRM), conversion rate, complication rates, time to first flatus passage, time to resume a soft diet and postoperative length of stay.

### 3.4.2 Postoperative surveillance

Patients were followed for at least five years. The assessment during follow-up included physical examinations of the body, rectal examination if needed, complete blood cell counts, and CEA levels every 3–6 months after operation. Additionally, abdominal ultrasonography, colonoscopy, and CT of chest, abdomen and pelvis, or MRI of abdomen and pelvis if necessary were arranged per 6–12 months after operation. The local recurrence of the tumor or distant metastasis was diagnosed according to the colonoscopy finding and biopsy results, CT, MRI, PET or whole-body bone scan if needed.



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## 3.5 Statistical methods

Descriptive statistics were used to analyze the data. For continuous parameters, percentages, frequencies, medians, means, standard deviations, and quartiles were analyzed using an independent *t*-test. Frequencies and percentages were analyzed using the chi-square test and Fisher's exact test for categorized parameters. We demonstrated the survival using the Kaplan–Meier curve and analyzed the factors influencing the survival curves using the log-rank test (Mantel–Cox). The multivariate logistic regression was used to determine independent prognostic factors which may be associated with radicality of CRM. The multivariate Cox regression was used to identify independent prognostic factors associated with 5-year DFS and OS rates. Statistical significance was set at a two-sided P-value of less than 0.05. All statistical analyses were performed using the Statistical Analysis System (SAS) version 9.4 for Windows.



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# Chapter 4 Surgical outcomes for the application of MIS in the treatment of cT4 LACRC

Controversy is still surrounding the application of laparoscopic surgery for treating cT4 LACRC. R0 resection is a critical curative treatment for CRC. Suspicious cancerous tissue was removed. When cT4 LACRC is encountered, surgeons require multivisceral en bloc resection. However, multivisceral resection requires surgical techniques, potentially compromising the safety and feasibility of laparoscopic surgery in patients with locally advanced cancer. Studies about the laparoscopic and open surgeries are limited with regard to the short-term intraoperative and long-term oncologic outcomes.[73,74] Therefore, according to the most updated NCCN guidelines, the laparoscopic surgery is still not advocated for treating LACRC considering the surgical risks and compromising the radicality.[15,16] Some large surgical societies still state conservatively that the open method is more appropriate than laparoscopic method in this scenario.

Considering the introduction of advanced optic systems and the maturation of laparoscopic skills, we believe that the application of MIS for cT4 LACRC deserved to be evaluated. This chapter describes the clinicopathological features of patients with LACRC who underwent MIS. We will assess the safety, feasibility, and efficacy of MIS for treating cT4 LACRC by analyzing the complications, conversion, mortality, postoperative recovery, and oncologic outcomes. These results will be compared with those of previous studies on laparoscopic and open surgery.



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## 4.1 Patients' demography and clinicopathology

A total of 128 patients with cT4 LACRC who underwent MIS for en bloc resection of primary CRC were included in the 13-year period. Figure 1 showed the recruitment and selection for patients with cT4 LACRC. Here, we found that clinical metastatic lesions (distant metastasis or peritoneal carcinomatosis) accounted for 29.7% of all cases. Clinical data of the 128 patients are presented in Table 3. Among them, 90 (29.7%) patients had cT4 LACRC without distant metastasis or peritoneal seeding. 26 (28.9%) patients had cT4a LACRC, and 64 (71.2%) had cT4b LACRC. The primary tumor site was predominantly the left side (Table 4). Four patients underwent preoperative chemoradiation therapy. The demographics and clinical parameters of the patients with cT4a and cT4b LACRC are listed in Table 4.

## 4.2 Results

### 4.2.1 Operative time and blood loss

The median operative time was 309 min and the median blood loss of 175 ml for the 128 patients with cT4 LACRC (Table 5). The mean operative time was 306.9 ± 72.6 mins, and the blood loss was 227.1 ± 242.7 mL for the 90 cT4M0 LACRC patients.

Among 90 cT4M0 LACRC patients, the mean operative time was 278.3 ± 72.7 mins for cT4a patients and 316.9 ± 70.3 mins for cT4b patients ($P$=0.1060). The mean blood loss was 118.7 ± 108.1 mL for cT4a patients and 264.3 ± 264.6 mL for cT4b patients ($P$=0.1626) (Table 6).



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### 4.2.2 Resected organs and concomitant procedure

The number of organs invaded by cT4a LACRC in the 90 cT4M0 patients is shown in Figure 2. Furthermore, we found that the urinary bladder (n=23), peritoneum (n=15), adnexa (including the ovary) in female patients (n=14), and the small bowel (n=9) were most frequently invaded by cT4 LACRC. Consequently, partial cystectomy (N = 23), peritonectomy (n=15), unilateral/ bilateral oophorectomy (N = 18), and small bowel resection (N = 9) were the most frequent concomitant procedures performed in this cohort (Figure 3).

### 4.2.3 Conversion

For 128 cT4 patients, open conversion was required in 10 patients (7.8%) (Table 5). For 90 cT4M0 LACRC patients, six (6.7%) open conversions were noted. Among them, there was one (3.9%) open conversion in the cT4a patient group and 5 (7.8%) in the cT4b patient group (*P*=0.4942). The characteristics of the patients who underwent open conversion are shown in Table 6.

### 4.2.4 Radicality

For 90 cT4M0 patients, 83 patients (92.2%) achieved R0 resection; R1 resection in six patients (6.7%), and R2 resection in one patient (1.1%).

In Figure 1, we found seven patients with R1 or R2 resection. One pT4b patient with R1 resection underwent open conversion to anterior resection, partial bladder resection, and left ureteral segmentectomy because the primary tumor invaded the left



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ureter and bladder underwent. One pT3 patient underwent R2 resection because the superior mesenteric vein trunk was encased by the primary tumor.

### 4.2.5 Recovery

For 90 cT4M0 LACRC patients, the mean time to flatus was 4.4 ± 3.2 days; the mean time to resume a soft diet was 7.4 ± 5.3 days. The mean postoperative length of stay was 15.3 ± 12.1 days. Among them, the mean time to flatus was 3.7 ± 1.2 days for cT4a patients and 3.6 ± 0.0 days for cT4b patients (*P*=0.0370). The mean time to resume a soft diet was 5.2 ± 2.0 days for cT4a patients and 8.1 ± 5.8 days for cT4b patients (*P*=0.0004). The mean postoperative length of stay was 10.8 ± 3.6 days for cT4a patients and 16.8 ± 0.0 mins for cT4b patients (*P*=0.0007). We found that delayed postoperative recovery occurred in cT4b patients compared to cT4a patients in terms of time to flatus, time to resume a soft diet, and postoperative length of stay.

### 4.2.6 Complications

Among the 90 patients with cT4M0 LACRC, 15 had class II, two for IIIA, four for IIIB, four for IVA, and one had IVB. Among the cT4a patients, three had II, one had IVA, and one had IVB. Among the cT4b patients, 12 were class II, two for IIIA, four for IIIB, and three for IVA. Anastomotic leakage occurred in seven patients, accounting for the most common complication after colectomy. Only one patient (0.78%) died in this cohort six days after surgery because of pulmonary embolism.



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### 4.2.7 Oncologic efficacy

The 3-year DFS and OS rates corresponded with oncologic outcomes proposed and predicted according to TNM staging (Figure 4). For stage II patients, the 3-year OS rate was 86.8% (95% confidence interval [CI]:0.725–0.964). For stage III patients, the 3-year OS rate was 57.9% (95% CI:0.414–0.736). And for stage IV patients, the 3-year OS rate was 17.8% (95% CI:0.036–0.398). Regarding the DFS rate, stage II was 86.1% (95% CI: 0.670–0.946); stage III was 54.1% (95% CI: 0.378–0.679); and stage IV was 10.8% (95% CI: 0.190–0.287).

As to the radicality, the 3-year DFS and OS were 70.3% (95% CI: 0.588–0.807) and 77.6% (95% CI: 0.663–0.872) for patients with R0 resection. While the 3-year DFS and OS were 28.6% (95% CI: 0.007–0.750) and 42.9% (95% CI: 0.113–0.781) for patients with R1/R2 resection, respectively. The 3-year DFS ($P$=0.0014) and OS ($P$=0.0003) were longer for patients with R0 resection than those with R1/R2 resection (Figure 5).

## 4.3 Discussion

The cT4 LACRC comprises two different scenarios: cT4a and cT4b. These two scenarios required different surgical treatments. The management of cT4a LACRC includes primary colorectal resection and radical lymphadenectomy, which is a procedure similar to that used for treating T3 CRC. However, cT4b LACRC requires multivisceral resection, which demands higher technical surgical requirements. In this context, we analyzed the outcomes separately and compared the results between patients with cT4a and cT4b LACRC.



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The present study showed that patients with cT4a LACRC undergoing MIS had satisfactory short-term results, including radicality, overall complications, and postoperative recovery, compared to previous studies. A large cohort study reported by Elnahas *et al.* used the database of the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) and included patients who underwent colorectal resection for stage T4 colon cancer.[41] This study excluded T4b LACRC because of the wide-ranging surgical management of T4b LACRC and found that the radicality of laparoscopic surgery for treating T4a LACRC was equivalent to that of open surgery.[41] Klaver *et al.* used the Dutch Surgical Colorectal Audit from 2009–2014 to evaluate the outcomes of conventional open surgery and laparoscopic surgery for treating LACRC with or without multivisceral resection. The authors found that the R0 rate for laparoscopic surgery without MVR was 96% and that for laparoscopic surgery with R0 rate was 93% compared to open surgery (89% and 86%, respectively).[29] Further, a meta-analysis conducted by the same author, Klaver *et al.*, included seven observational studies and performed a subgroup analysis of patients with pT4a LACRC s undergoing either laparoscopic surgery or open surgery. The results indicated that the radicality and oncologic outcomes of laparoscopic surgery were equivalent to those of open surgery for the treatment of pT4a LACRC. Based on these studies, we conclude that laparoscopic surgery is a safe, feasible, and efficacious method for treating cT4a LACRC. Furthermore, based on the results of previous randomized controlled clinical trials that included cT4a LACRC[6,7,9,34,75], a large population-based study [29,41] and a meta-analysis [74], we suggest that the evidence level is IB. This was a high-quality, randomized, controlled study without bias. We also echoed the conclusion made by Klaver *et al.* that the improvement of laparoscopic surgery for the treatment of LACRC requires optimized preoperative



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imaging, routine multidisciplinary team discussion, and centralization and specialization of medical services.[29]

Our study further analyzed cT4b LACRC cases that required multivisceral resection. For these patients, using laparoscopic surgery to perform multivisceral resection is technically more complex than using cT4a LACRC. If reconstruction is required after the resection of the invaded structures or organs, the technique is technically demanding and usually requires open conversion.

We performed a systematic literature review to determine the current status of MIS for the treatment of cT4b RC requiring multivisceral resection. By searching MeSH descriptors including “laparoscopic surgery”, “minimally invasive surgery”, “robotic surgery”, “cT4b”, “locally advanced colorectal cancer” and “multivisceral resection” in PubMed and excluding CRC with distant metastasis, we found 10 studies that reported their results on cT4b LACRC requiring MIS for multivisceral resection. These relevant studies were mostly case series and retrospective in nature.[39,48,56,73,74,76-82] Seven reports were of laparoscopic surgery, while three reports were regarding robotic surgery. Nagsue *et al.* included 126 patients with cT4b LACRC who underwent multivisceral resection. Among them, 60 patients underwent laparoscopic surgery, and 66 underwent open surgery. The conversion rate in the laparoscopic group was 6.7%. The R0 rates were 95% and 98.5% in the laparoscopic and open surgery groups, respectively. Kumamoto *et al.* reported a case series of 118 patients who underwent laparoscopic multivisceral resection for primary colon cancer, attaching to or invading nearby structures or organs. Fifty-four patients (45.38%) were pathologically confirmed as having pT4b cancer. Mukai *et al.* reported 69 patients with locally advanced colon cancer who underwent laparoscopic surgery for multivisceral resection. Among them, 34 (49.3%) patients had pT4 colon



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cancer. Less than half of the patients had pT4b LACRC. The preliminary results of this case series showed that laparoscopic surgery is a safe and feasible method for treating cT4b LACRC that requires multivisceral resection. Some authors have also admitted that the laparoscopic approach can only be performed in selected patients. For example, cT4b LACRC invading the ureter require open conversion for ureter reconstruction.[48] Most studies on robotic surgery are case series or case reports.[80-82]

A review article conducted by Ishiyama *et al.* analyzed six studies regarding laparoscopic surgery for cT4b LACRC that required multivisceral resection, showing that laparoscopic surgery has oncologic outcomes comparable to those of open surgery. The pT4b percentages were 28.9–78.9%. The conversion rate was 2.89–20.8%. The R0 rate was 97.4–86.8%. The total complication rate was 10.5–21.1%. However, the authors concluded that randomized studies should be conducted.

We also found that the lack of data on long-term survival in these studies makes it difficult to justify the long-term benefits of MIS. Kim *et al*. reported that the 5-year OS rate was approximately 60.0% for stage II and 58.3% for stage III CRC patients.[77] We suggest that long-term survival data, including DFS and OS at each stage of CRC, should be reported in future studies.

Based on the results of previous studies and the present study regarding cT4b LACRC, we found that most organs invaded by cT4 LACRC were different (Figure 6). Most structures or organs involved in the primary cancer were the abdominal wall or peritoneum, small bowel, urinary bladder, and ovaries (Figure 6).[39,48,56,73,76-80,82,83] For laparoscopic surgery, concomitant resection of these structures/organs can be performed, although with different surgical difficulties. Some structures/organs listed above only



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required resection, including the abdominal wall, peritoneum, Gerota fascia (peri-renal fat), or adnexa. However, some organs require repair or reconstruction, including the small bowel and the urinary tract.

In this context, the structure and organs invaded by primary CRC can serve as a guide for the application of MIS. Wasmann *et al.* classified clinically distinct categories of multivisceral resection by analyzing 130 patients with T4b colon cancer who underwent open resection with curative intent. He divided multivisceral resection into four categories: gastrointestinal tract, urologic organs (bladder and ureter), solid organs (spleen, kidneys, liver, pancreas, and uterus), and abdominal wall, omentum, and ovaries.[84] According to Wasmann's classification, we suggest that MIS synchronous multivisceral resection can be performed for the following structures and organs: gastrointestinal tract (e.g., small bowel), urologic organs (e.g., urinary bladder with trigone-sparing), solid organs (e.g., uterus), and abdominal wall/omentum/ovaries. The level of evidence was classified as IC.

The present study shows that LACRC is a heterogeneous disease. The surgical management of cT4 LACRC should be tailored according to cT4a/cT4b status. Recent studies have confirmed the safety, feasibility, and efficacy of laparoscopic surgery for the treatment of cT4a LACRC. Regarding cT4b LACRC requiring multivisceral resection, MIS should be performed with caution. Our study suggests that laparoscopic surgery may be performed in selected patients with cT4b LACRC who require concomitant organ resection. These organs included the urinary bladder (trigone-sparing), small bowel, adnexa, peritoneum, and Gerota's fascia. However, the true benefits of MIS for treating cT4b LACRC invading the above-mentioned organs require high-level studies.



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# Chapter 5 Surgical outcomes of robotic versus laparoscopic surgery for LACRC invading the urinary bladder

Our previous chapter has demonstrated that laparoscopic surgery for CRC confers improved postoperative outcomes for treating cT4a LACRC when compared with cT4b patients[85], with similar oncologic outcomes with those of open surgery in previous studies.[29,41] Our study has also showed that laparoscopic multivisceral resection is safe and feasible in selected patients with cT4b LACRC, such as the urinary bladder (trigone-sparing), small bowel, adnexa, peritoneum, and Gerota's fascia, with satisfactory results.[86]

The urinary bladder is one of the organs most frequently affected by CRC because of its proximity.[87] Simultaneous colectomy and surgical extirpation of the invaded wall of urinary bladder are necessary once the cT4b LACRC invading the urinary bladder was encountered. Current opinions suggest open surgery the standard surgical approach for treating LACRC with urinary bladder invasion. The procedures of concomitant resection of primary CRC and contagious urinary bladder were technically complex by using open surgery.[88-94] If the trigone area of urinary bladder is invaded by the tumor, the simultaneous reconstruction of the urinary tract after the partial or total cystectomy became necessary. Owing to the high technical demanding in this circumstance, open surgery is the preferred method.[91]

Robotic Da VinCi surgery has become a popular method for the treatment of CRC. Robotic surgery enables surgeons to perform meticulous tasks such as repair and knotting, which are considered challenging in laparoscopic surgery. Robotics presents an



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alternative to multivisceral resection in the same surgery, with potentially favorable outcomes. However, studies of robotic multivisceral resection are limited. [95-98]

Inspired by such advancements in robotic surgical technology, we aimed to assess the applicability of robotic surgery in the treatment of cT4b LACRC with urinary bladder invasion. We also aimed to evaluate whether robotic surgery could regenerate the technical merits and oncologic benefits of laparoscopic surgery for treating LACRC invading the urinary bladder.

## 5.1 Patients' demography and clinicopathology

A total of 41 patients were recruited for this study. Twenty-two patients underwent laparoscopic surgery, while nine patients underwent robotic surgery (Figure. 7). Among 32 patients undergoing laparoscopic surgery, 25 patients were pT4a and seven patients were pT4b. Among nine patients underwent robotic surgery, four patients were pT4a and five patients were pT4b. No statistically significant differences was noted between the groups in terms of the clinical features (Table 11).

## 5.2 Results

### 5.2.1 Operative time and blood loss

The mean operative time for the 32 patients who underwent laparoscopic patients was 353.24 ± 73.98 mins. Blood loss was 315.00 ± 304.32 mL. For nine robotic patients, the mean operative time was 387.33 ± 200.62 mins, and the mean blood loss was 171.11



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± 133.08 mL. There were no significant differences between the two groups in terms of operative time and blood loss.

### 5.2.2 Conversion

There were four (12.5%) open conversions in the laparoscopic group and one (11.1%) open conversion in the robotic group. In laparoscopic group, open conversion was performed in three patients: inability to stopping bleeding laparoscopically in one patient, trigone invasion in one patient, and left ureters invasion in two patients. In the robotic group, one patient underwent open conversion because left ureter was invaded by the tumor requiring ureteral reconstruction.

### 5.2.3 Radicality

We evaluated the radicality of CRM for these patients. The R0 resection rate in the laparoscopic group accounted for 87.50% whereas 55.56% in the robotic group (Table 12). Multivariate regression analysis demonstrated that the surgical approach was not an increased prognostic factor for the radicality of CRM (Table 13).

### 5.2.3 Complications

There were no significant differences between the two groups with regard to complication rates, time to flatus passage, or postoperative length of stay (Table 12).



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### 5.2.4 Oncologic efficacy

The mean follow-up period was 40.8 months. Six pM1 patients were excluded from the survival analysis, including three in the laparoscopic group and three in the robotic group. No statistically significant difference between two groups was observed in terms of the 5-year DFS rate (64.64% vs. 62.50%, $P$=0.6221) and OS rate (75.30% vs. 83.33%, $P$=0.9842) (Figure 8).

Multivariate Cox regression analysis demonstrated that R1 resection was the only negative independent prognostic factor that lowered the 5-year DFS rate (hazard ratio, 21.386; 95% CI, 1.991–229.723; $P$=0.0115) (Table 13).

## 5.3 Discussion

cT4b LACRC is a clinically challenging disease. The invaded organs are heterogeneous; therefore, surgical strategies for these advanced tumors are wide-ranging. Some procedures require multivisceral resection and reconstruction, which is difficult, even with open laparotomy. Therefore, some surgeons discourage MIS in such cases. According to the findings in the previous section, some studies have shown that laparoscopic surgery is a safe and feasible method for cT4b invasion of the urinary bladder. In this chapter, we narrow the focus to a specific condition: cT4 LACRC with the invasion of the urinary bladder.

Our results showed that the tumor most often invaded the dome of the urinary bladder during laparoscopic surgery. The primary tumor and involved urinary bladder were simultaneously resected. Defects in the urinary bladder can be repaired with



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laparoscopic intracorporeal sutures using either Vicryl sutures or barbed V-loc sutures. Our study suggests that laparoscopic multivisceral resection combined with reconstruction is technically feasible if the invaded structures are the dome of the urinary bladder, with trigon-sparing.

Some retrospective case series have reported that laparoscopic colectomy with concomitant resection of the urinary bladder can be performed by experienced surgeons and exhibits acceptable short-term surgical results.[83] However, these reports were retrospective in nature and were case series.[80,83] Mukai *et al*. reported 17 laparoscopic multivisceral resections for the urinary bladder of cT4b LACRC, one of which required open conversion because of an abscess around the tumor and hard fibrosis.[79] Miyo *et al*. reported six laparoscopic multivisceral resections for urinary bladder invasion, one of which required open conversion due to tumor invasion to the trigone.[56] Miyake *et al.* reported five laparoscopic multivisceral resections of the urinary bladder, two of which required open conversion due to massive adhesion to the urinary bladder.[76] The other two case series conducted by Zhang *et al*. and Kim *et al.* reported 18 and 6 patients undergoing laparoscopic (including hand-assisted laparoscopic surgery) multivisceral resection of the urinary bladder, respectively. However, the number and details of the conversion were not mentioned.[77,78] In view of our results and those of previous studies, we suggest that cT4b LACRC with the invasion of the urinary bladder can be performed using laparoscopic surgery. Additionally, open conversion is acceptable to achieve a clear margin in cases of severe adhesion or trigone involvement.

Recent advancements in robotic surgery represent an alternative to simultaneous multivisceral resections. The dexterity of robotic wrists complements the shortages of laparoscopic instruments. Some case reports and case series have described simultaneous



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surgical procedures. Piccoli *et al*. reported on 11 patients who underwent total robotic multivisceral surgery. Among them, six patients underwent surgery for double cancer, mostly CRC and urological malignancy.[98] The author advocated the possibility of a multidisciplinary platform in which the robotic system allowed two specialists to perform simultaneous multivisceral resection. The results were satisfactory. Our current study is one of the largest surgery reports to evaluate laparoscopic vs. robotic surgery for treating patients with cT4b LACRC invading the urinary bladder in terms of surgical and oncologic outcomes. The results of this study provide valuable information on this topic. We further suggest recruitment of more patients is mandatory to elucidate the applicability of robotic surgery in this patient group.

In our study, the R1 rate was slightly higher in the robotic group than that in the laparoscopic group, although the difference was not statistically significant. The small number of robotic surgery cases may explain the results of our study. Moreover, the learning curve of robotic surgery may confound the performance of robotic multivisceral resections. The recruitment of more patients is mandatory for future studies to justify the surgical indication of robotic surgery and the cost-effectiveness of robotic surgery in overcoming the technical learning curve when encountering T4b LACRC.

In summary, the current study demonstrated that urinary bladder invasion by cT4b LACRC, including laparoscopic and robotic surgery, could be a candidate for MIS. Both laparoscopic and robotic surgeries can be safely and feasibly performed for treating cT4b LACRC invading the urinary bladder. The preliminary results in this study showed significant complication rates, radicality, and oncologic outcomes similar to those reported in previous studies. Moreover, robotic surgery harbors the technical advantages of intracorporeal reconstruction despite our study showing similar results between robotic



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and laparoscopic surgery. Thus, we suggest that robotic surgery should be included in a multidisciplinary approach to treating LACRC, especially the cT4b LACRC requiring multivisceral resection and complex reconstruction.



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# Chapter 6 Future prospects

From the preceding chapters of the present dissertation, we found that MIS can be performed to treat LACRC with satisfactory surgical and oncologic outcomes. However, some specific issues still need to be further addressed, including the role of laparoscopic surgery for cT4a and cT4b LACRC, a definite indication of robotic surgery for LACRC requiring multivisceral resection, and clinical implications of neoadjuvant chemoradiation therapy in the era of MIS.

## 6.1 The role of laparoscopic surgery for cT4a LACRC

Our study showed that laparoscopic surgery is safe, feasible, and efficacious for LACRC, particularly in the presence of peritoneal penetration (cT4a/pT4a). Among the patients with cT4 LACRC in our cohort, 70 (84.3%) had stage ≤ pT4a. In this situation, the resectability of T4a tumors with R0 resection is similar to that of T3 tumors. The serosal ingrowth of the cancer was confined to the visceral peritoneum. Standard colectomy did not compromise the circumferential margins, and no concomitant resection of the organ was required.

Here, we address the importance of differentiating cT4a/pT4a from cT4b/pT4b LACRC because surgical complexity differs. The latter procedure requires multivisceral resection and reconstruction. Future studies that intend to analyze the surgical outcomes of MIS and open surgery for high-quality levels should consider the differentiation of cT4a/pT4a and cT4a/pT4b LACRC in the inclusion/exclusion criteria of future studies or the balancing of the proportions of cT4a/pT4a and cT4b/pT4b.



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## 6.2 The role of laparoscopic surgery for cT4b LACRC

When cT4b LACRC is encountered, multivisceral resection is always required to achieve R0 resection. In Chapter 4, our study showed that laparoscopic surgery is safe, feasible, and efficacious in selected patients with LACRC. We further identified the criteria that may potentially benefit from MIS. If the invaded organs are the urinary bladder, adnexa, small bowel, and abdominal wall/parietal peritoneum, laparoscopic surgery can be a safe, feasible, and efficacious method for the simultaneous resection of primary CRC and the invaded organs to achieve satisfactory R0 rates with acceptable conversion, complications, and mortality. The proposed surgical plan for LACRC is outlined in Figures 9 and 10, respectively.

The current evidence regarding the application of laparoscopic surgery for cT4b LACRC is IC. All previous studies on this topic were restricted to nonrandomized reports. Further randomized controlled studies are needed to validate the application of MIS in the treatment of cT4b LACRC. Because of the heterogeneity of organs invaded by cT4b LACRC and the wide range of surgical strategies, we suggest that future studies should be conducted using organ-oriented designs. The control group was matched to the invaded structures/organs.



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## 6.3 The robotic surgery in cT4b LACRC requiring multivisceral resection and reconstruction

This study sheds light on the role of robotic surgery in the treatment of cT4b LACRC that invades the urinary bladder.[99] Robotic surgery has two advantages for multivisceral resection. First, the dexterity of endowrists allows the surgeon to perform intracorporeal repair and knotting, enabling simultaneous reconstruction without the need for conversion. Second, robotic surgery offers a multidisciplinary platform that allows procedures of different specialties to be completed simultaneously in the same surgery, thus reducing the exposure to anesthetic agents, hospitalization frequency, morbidity, and cost-effectiveness on an economic basis.[98]

Some attempts have been made to use robotic surgery for cT4b LACRC requiring multivisceral resection but are only limited to case reports.[80,82,100-103] Most cases are primary rectal cancer, and most invaded organs are the prostate, vagina, and urinary bladder. Additional data are required to justify the role of robotic surgery for multivisceral resection and reconstruction.

The learning curve may confound surgeons' performance in performing multivisceral resection of cT4b LACRC.[104] In general, a minimal 19–128 cases are required to achieve satisfactory results of robotic colectomy for treating CRC.[105] However, robotic multivisceral resection is more difficult to perform than simple colectomy. The learning curve for robotic multivisceral resection is challenging because a more complex task should be performed. More data from surgeons skilled in robotic surgery and those who have passed the learning curve will elucidate the true benefits of the novel techniques for cT4b LACRC.



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This study suggests that MIS, including laparoscopic and robotic surgery, should be incorporated into surgical armamentaria for the treatment of LACRC in select patients. However, more patients are required to clarify the efficacy of robotic surgery.

## 6.4 Neoadjuvant chemoradiation therapy for rectal cancer

Nowadays the most common treatment algorithm for locally advanced rectal cancer (clinical stage T3-4 or N-positivity) is neoadjuvant chemoradiation therapy (nCRT) plus sequential radical resection.[106,107] Significant advantages of nCRT are that it lowers the local recurrence rate  and minimizes toxicity compared to postoperative radiotherapy. [108] [109] Additionally, nCRT can provide better local control by enhancing the effect of tumor shrinkage, which potentiate the sphincter-preserving surgery. Further nCRT can decrease the toxicity of chemoradiation therapy, hence lead to better compliance.[106,110]

According to the updated NCCN guidelines in 2022, the patients with locally advanced rectal cancer who underwent nCRT and radical resection are obliged to undergo six-month perioperative adjuvant chemotherapy, irrespective of the postoperative pathological staging.[107] The rationale of the suggestion is grounded in the conjecture that the benefit of postoperative adjuvant chemotherapy for patients with stage III colon cancer can be extrapolated to patients with stage III rectal cancer.[111,112] Additionally, the rationale of these guidelines inherited from the notion that the patients with Dukes' B and C rectal cancer undergoing radical resection of the rectum can benefit from adjuvant fluorouracil for improved OS before the era of preoperative radiation.[113]  Yet these speculations have never been directly proven.[112,114]



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In our study, the rate of nCRT was low in patients with rectal cancer. One reason for this is that most primary cancers are located proximal to the rectosigmoid junction. In the current guidelines, nCRT is not indicated for such a group of patients. Second, many patients with locally advanced rectal cancer experience tumor shrinkage after nCRT and were not included in our study because multivisceral resection is not indicated.

## 6.5 Neoadjuvant chemotherapy for unresectable colon cancer

Our study did not include patients with unresectable colon cancer. Adjuvant chemotherapy in these patients is beyond the scope of this study. According to the current National Comprehensive Cancer Network guidelines, neoadjuvant chemoradiation therapy is needed for current NCCN guidelines. The standard treatment regimen is oxaliplatin-based chemotherapy.[15]

Emerging evidence has demonstrated the benefits of neoadjuvant chemotherapy in locally advanced colon cancer. Gosavi *et al*. conducted a meta-analysis, showing that neoadjuvant chemotherapy might increase the likelihood of the R0 rate in T3/4 advanced colon cancer. The author pointed out that the pooled relative risk was 0.47 with a 95% CI and no increased adverse consequences of surgical complications, such as an anastomotic leak, wound infection, or reoperation rate.[115] In our opinion, neoadjuvant chemotherapy may also have potential benefits for converting unresectable cT4b LACRC into resectable cT4b LACRC by tumor downstaging, thus increasing the R0 resection rate. However, its actual benefits are still under investigation.



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# FIGURES

Figure 1. Recruitment and selection for patients with cT4 LACRC in cohort one

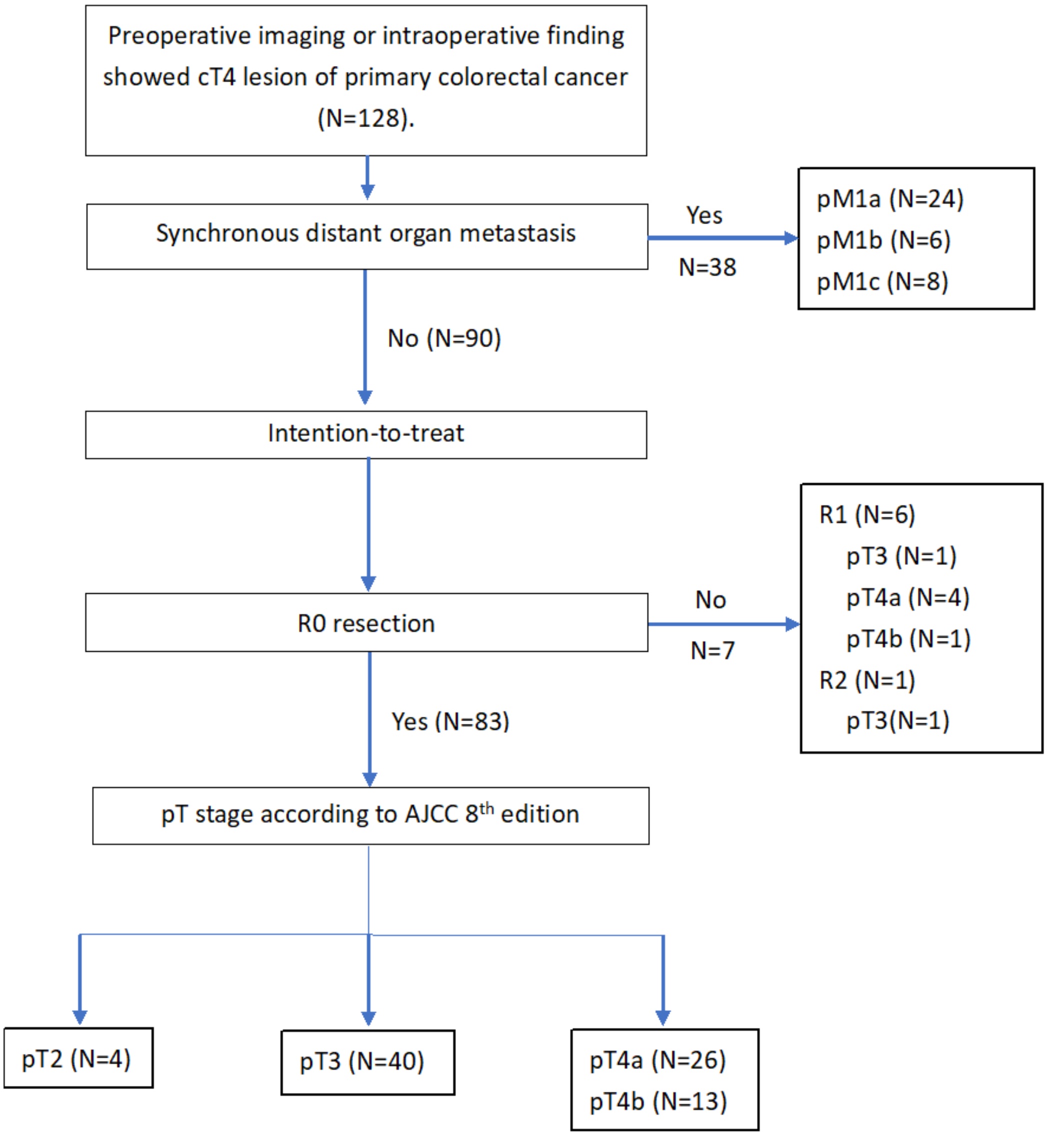




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Figure 2. Numbers of concomitant organ resected for cT4b LACRC (n=64) in cohort one

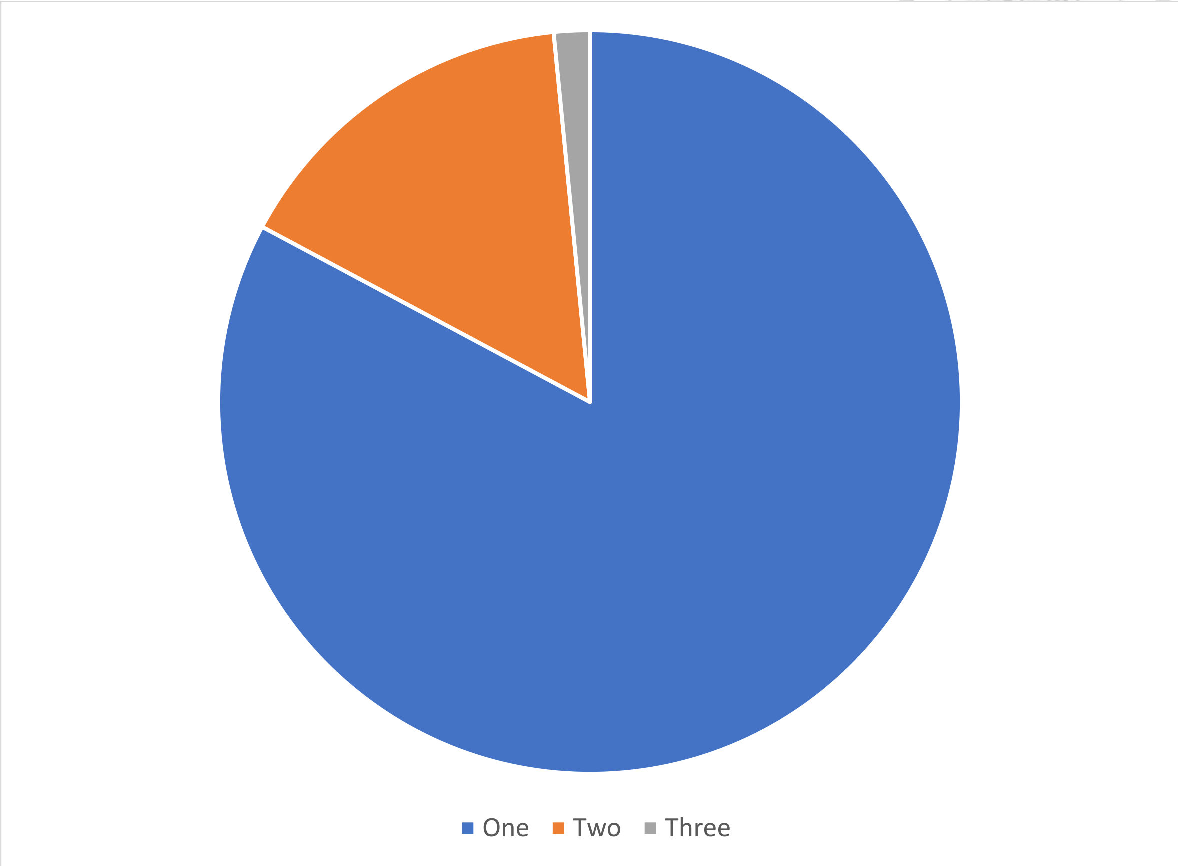




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Figure 3. The organs invaded by cT4b LACRC (n=64) in cohort one

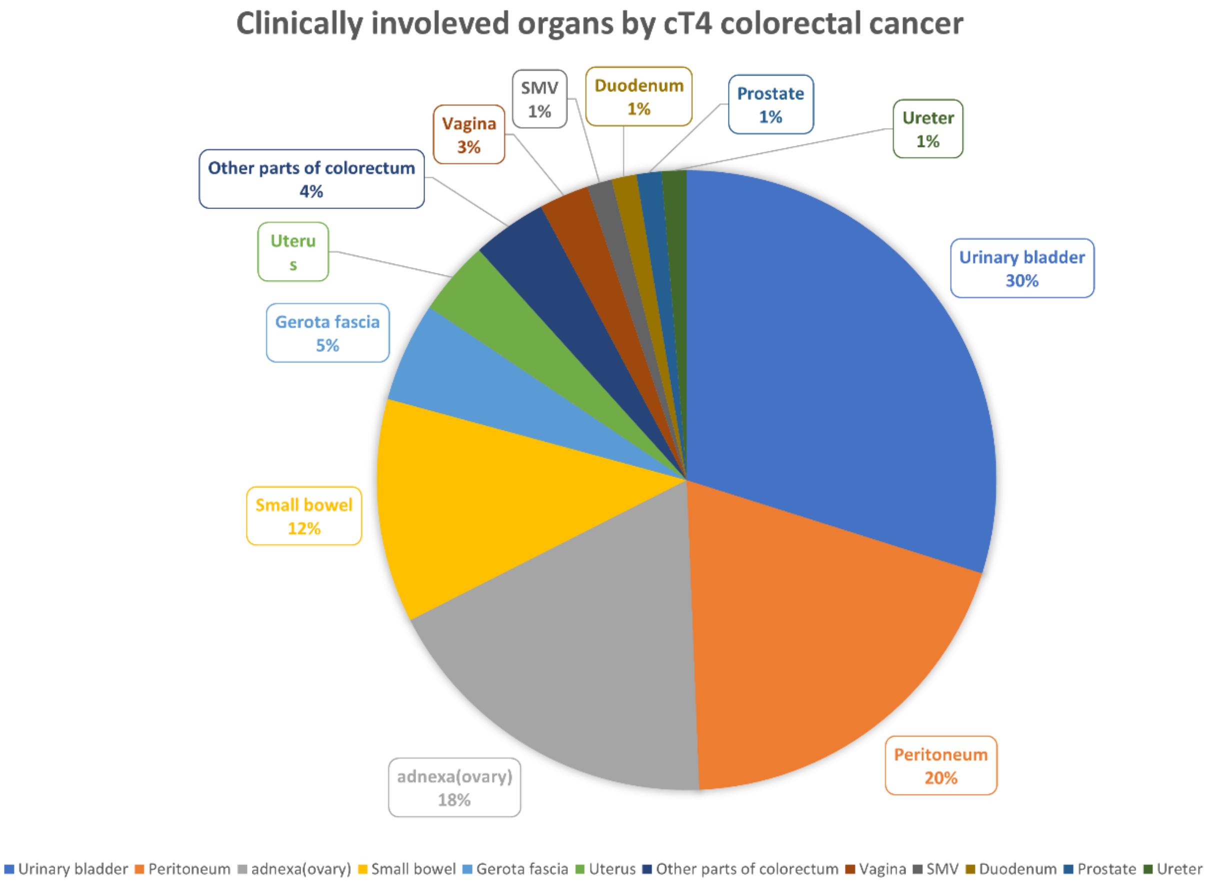




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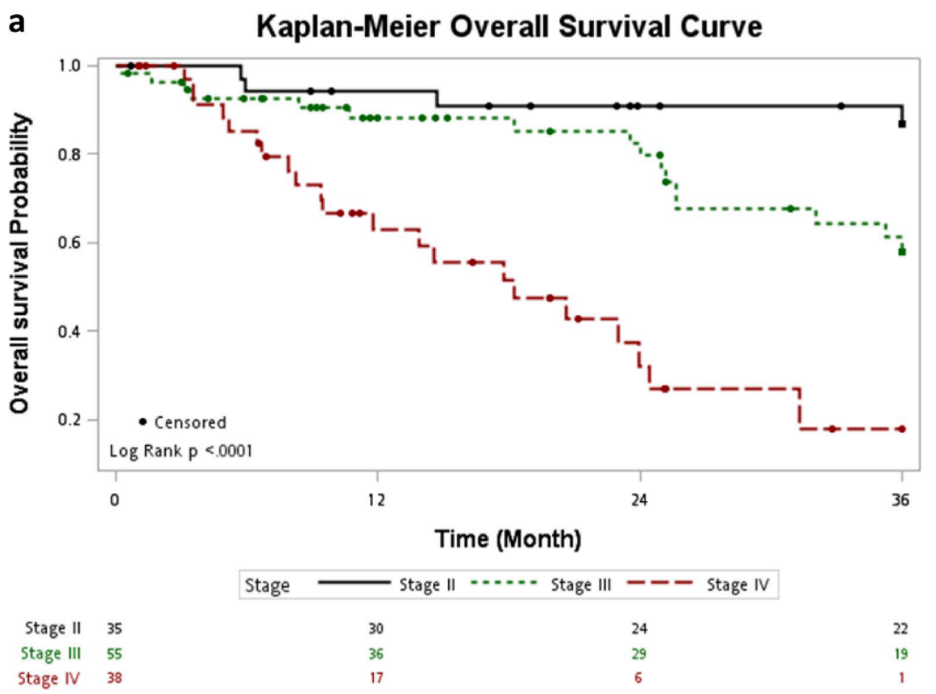
Figure 4. Survival of cT4 LACRC according to the TNM stages for all 128 patients (including M1) in cohort one. (a) Overall survival. (b) Disease-free survival



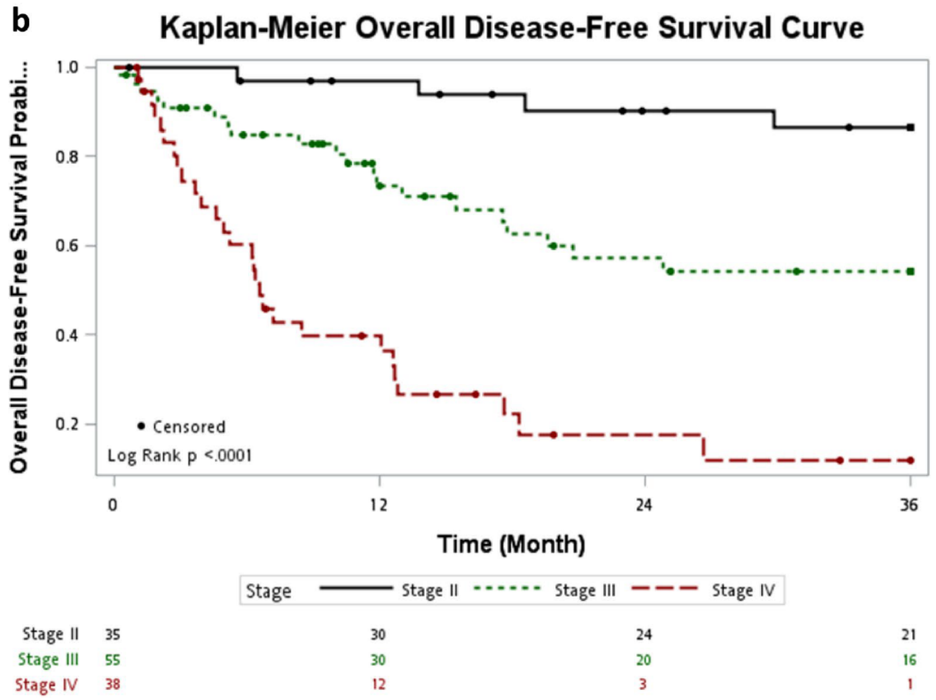






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Figure 5. Survival of cT4 LACRC according to the radicality in cohort one (n=90) (a) Overall survival. (b) Disease-free survival

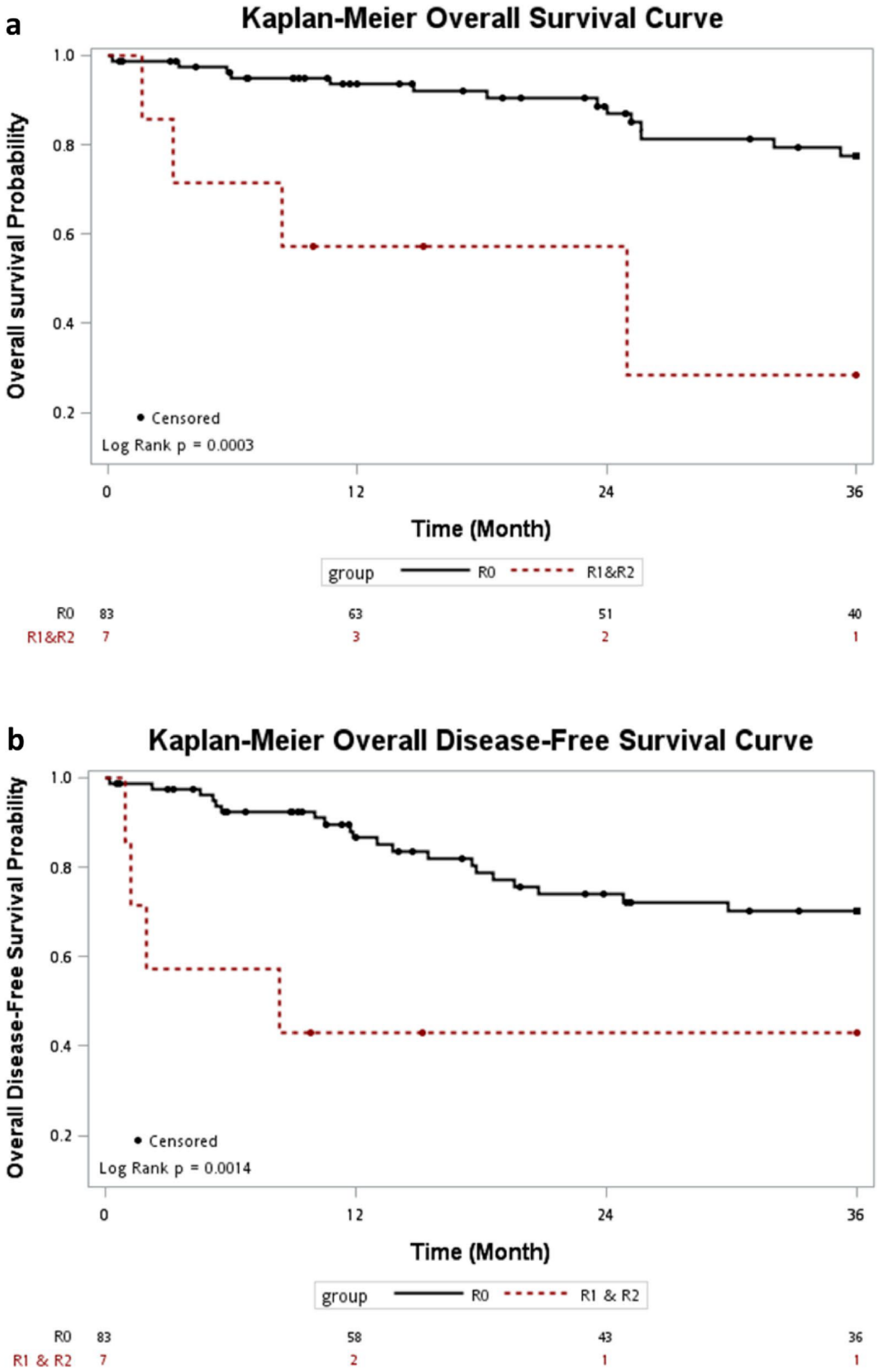




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Figure 6. The organ or structure invaded by cT4b LACRC in literature

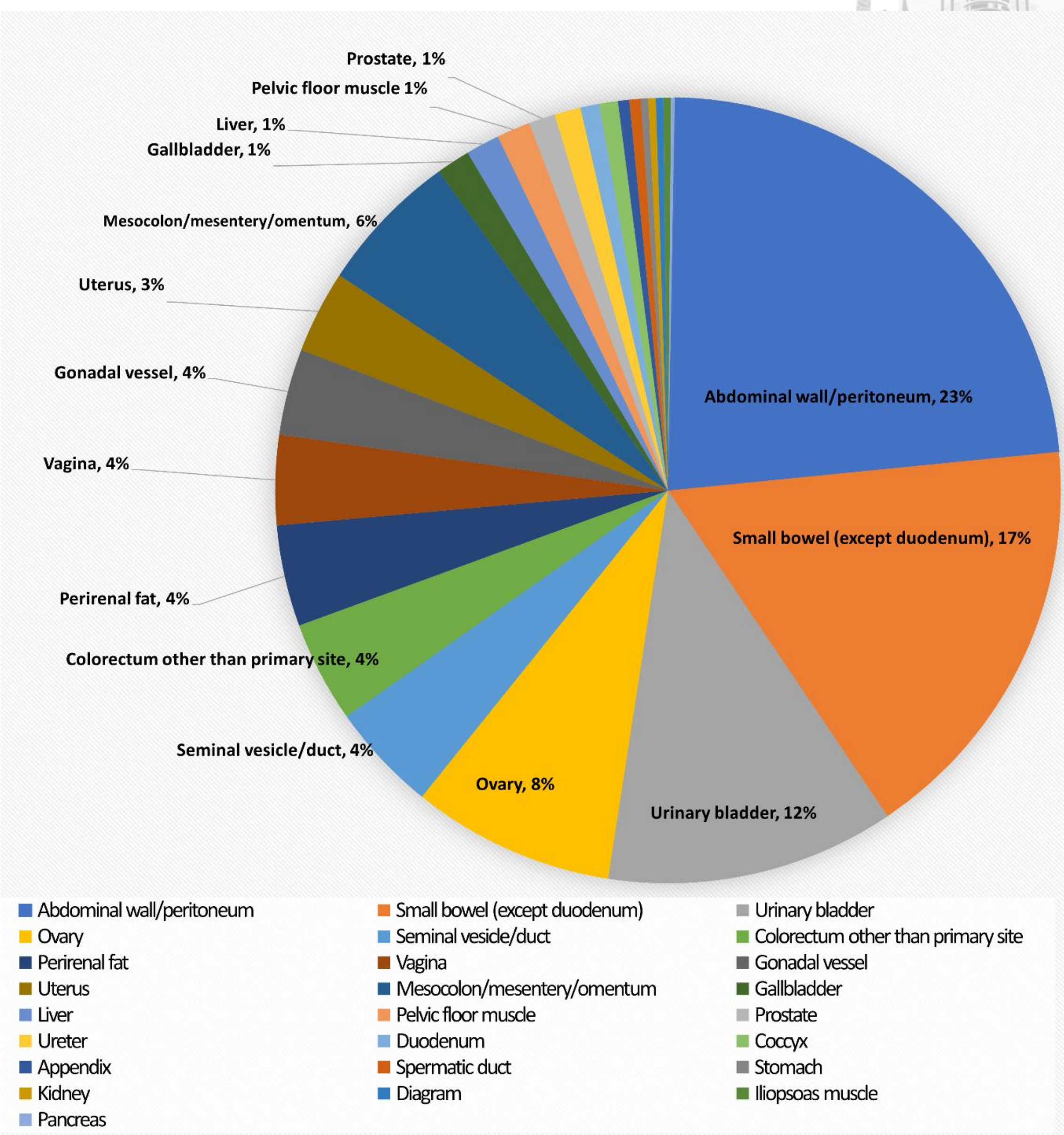




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Figure 7. Flowchart of the patient accrual of cT4b LACRC invading the urinary bladder on cohort two

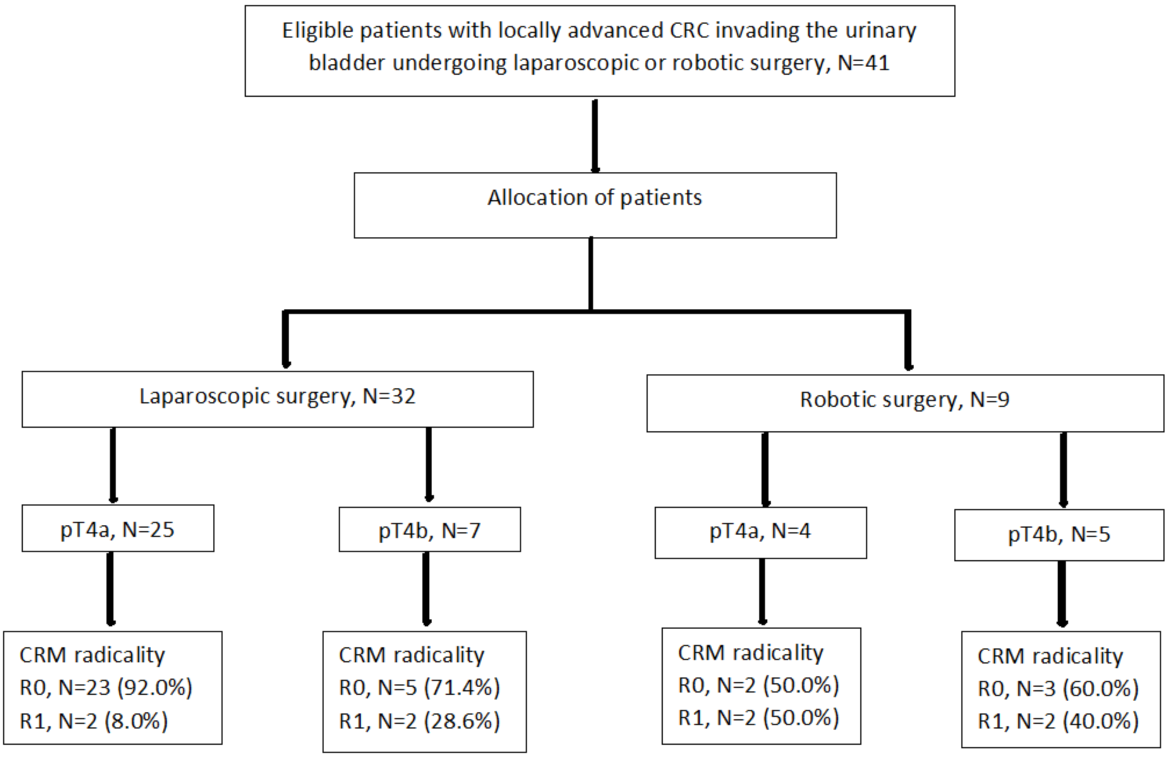




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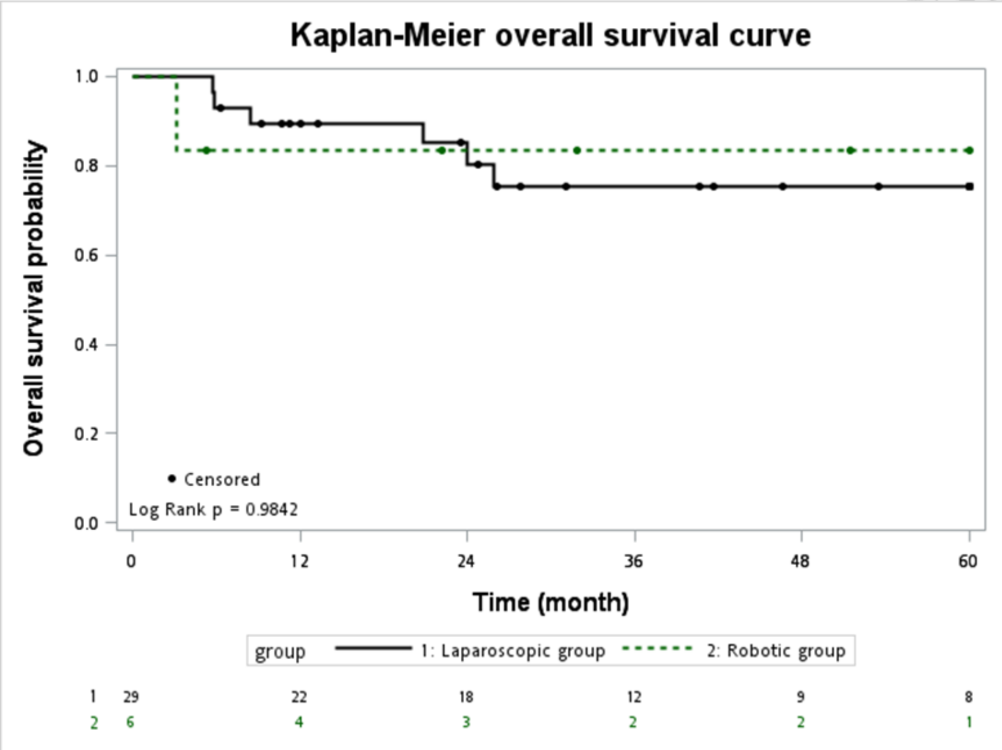
Figure 8. Survival of laparoscopic vs. robotic surgery for cT4b LACRC invading the urinary bladder in cohort two



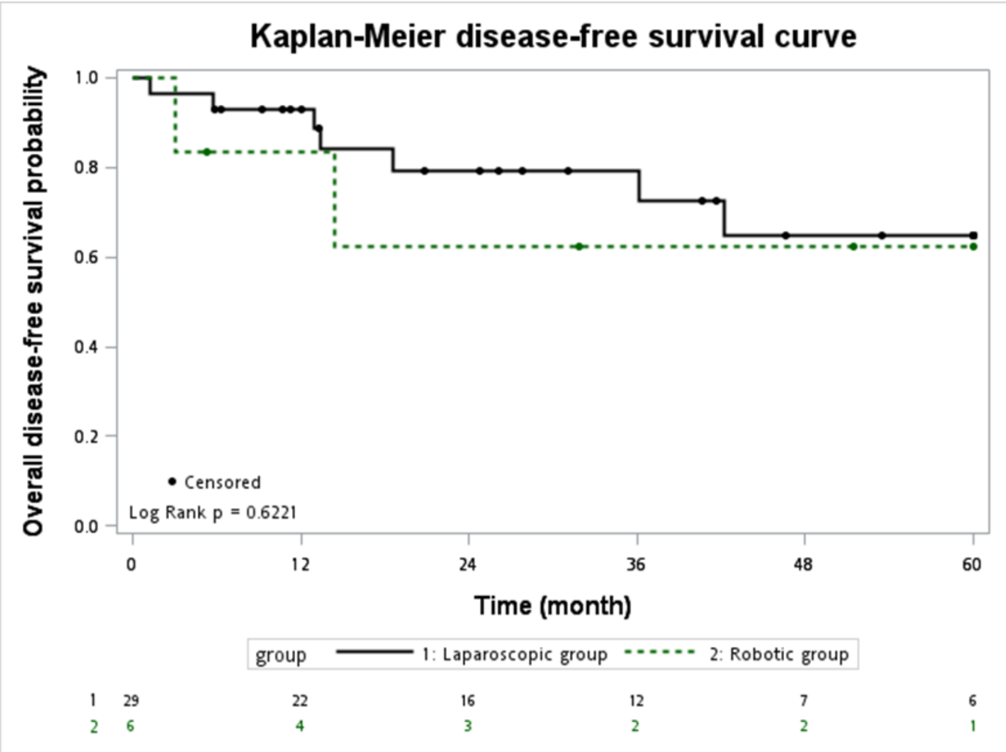






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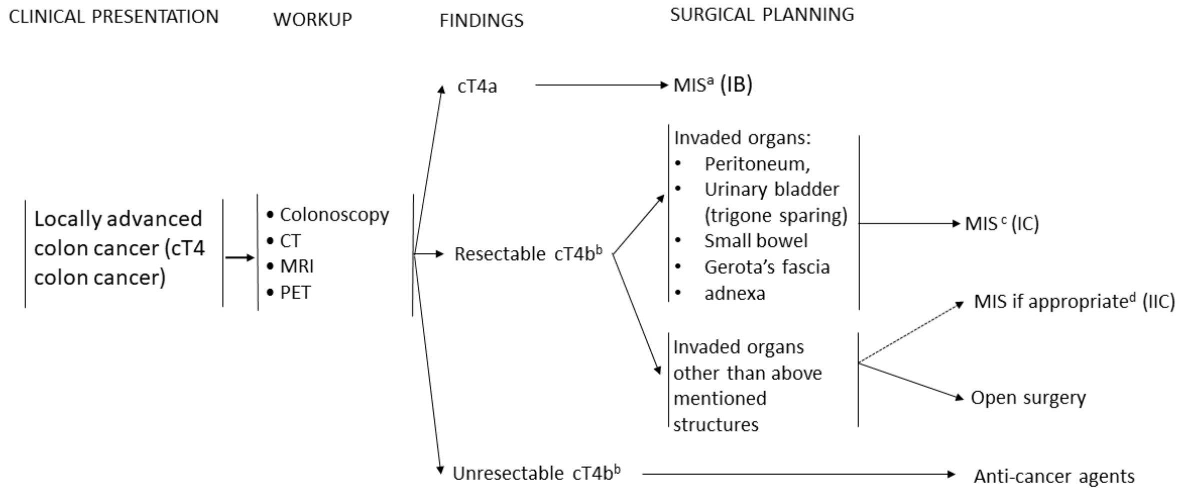
Figure 9. The proposed surgical planning for the management of locally advanced colon cancer




[a] MIS, minimally invasive surgery, including laparoscopic or robotic approach, evidence level IB
[b] According to surgeons' discretion on radicality
[c] Evidence level IC
[d] Evidence level IIC



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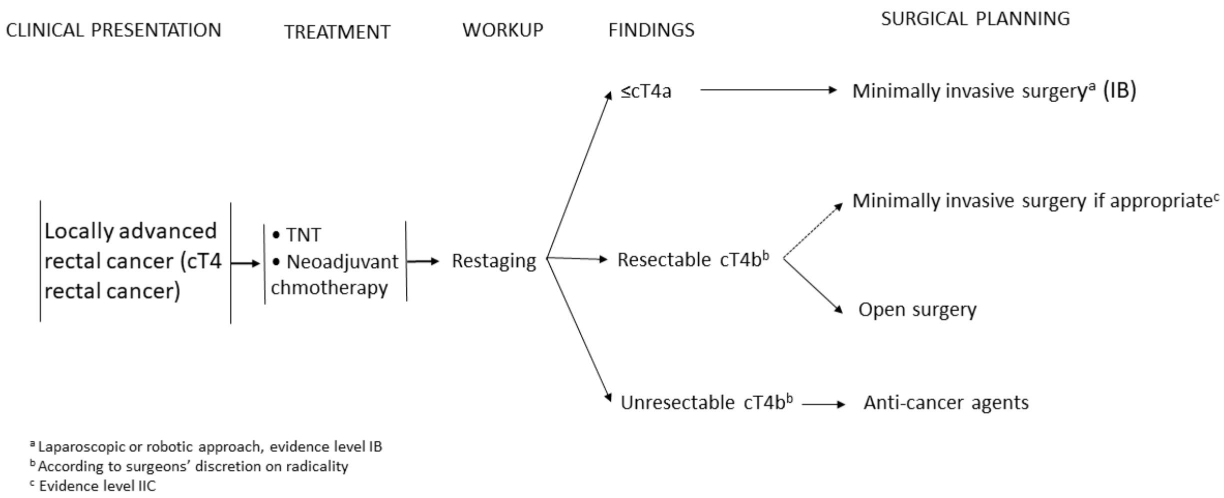
Figure 10. The proposed surgical planning for the management of locally advanced rectal cancer



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# TABLES

Table 1. The Grading of Recommendations, Assessment, Development, and Evaluation system

| | Description | Benefit vs risk and burdens | Methodologic quality of supporting evidence | Implications |
|---|---|---|---|---|
| 1A | Strong recommendation, high-quality evidence | Benefits clearly outweigh risk and burdens or vice versa | RCTs without important limitations or overwhelming evidence from observational studies | Strong recommendation, can apply to most patients in most circumstances without reservation |
| 1B | Strong recommendation, moderate-quality evidence | Benefits clearly outweigh risk and burdens or vice versa | RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or exceptionally strong evidence from observational studies | Strong recommendation, can apply to most patients in most circumstances without reservation |
| 1C | Strong recommendation, low- or very low-quality evidence | Benefits clearly outweigh risk and burdens or vice versa | Observational studies or case series | Strong recommendation but may change when higher quality evidence becomes available |
| 2A | Weak recommendation, high-quality evidence | Benefits closely balanced with risks and burdens | RCTs without important limitations or overwhelming evidence from observational studies | Weak recommendation, best action may differ depending on circumstances or patients' or societal values |
| 2B | Weak recommendation, moderate-quality evidence | Benefits closely balanced with risks and burdens | RCTs with important limitations (inconsistent results, methodologic flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies | Weak recommendation, best action may differ depending on circumstances or patients' or societal values |
| 2C | Weak recommendation, low- or very low-quality evidence | Uncertainty in the estimates of benefits, risks, and burden; benefits, risks, and burden may be closely balanced | Observational studies or case series | Very weak recommendations, other alternatives may be equally reasonable |



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Table 2. Literature reviews regarding the laparoscopic surgery for LACRC

| Reference | N | Inclusion criteria | Exclusion criteria |
|---|---|---|---|
| Hu *et al*. (2012)[38] | 24 | Potential curative surgery for a suspected T4 colorectal cancer | Not mentioned |
| Nagasue *et al*. (2013)[39] | 60 | En bloc resection of primary colorectal cancer with adjacent organs or structures because of intraoperative suspicion of direct invasion to adjacent organs or structures | Emergency surgery; synchronous resection of liver metastases |
| Vignali *et al*. (2013)[40] | 70 | Histologically proven T4 colon cancer | Rectal resection; emergency procedure |
| Elnahas *et al*. (2015)[41] | 61 | Relevant ICD v.9 codes 153.1-9, 154.0-3, and 154.8. Current procedural terminology codes 44139-147, 44150-151, 44155-156, 44160, 44204-208, and 44210-213 | T4b colonic tumors; locally advanced tumors below the peritoneal reflection |
| Shukla *et al*. (2015)[42] | 51 | Both genders; age ≥18 years; a T4 cancer on final pathologic examination of the specimen; curative-intent surgery | Distant metastases |
| Kim *et al*. (2016)[43] | 106 | Histologically confirmed colon cancer; major colon resection | Distant metastasis; familial adenomatous polyposis; hereditary nonpolyposis colorectal cancer |
| De' Angelis *et al*. (2016)[44] | 71 | pT4 colon cancer on final pathologic examination; stage II (T4a/T4b, N0, M0) or TNM stage III (T4a/T4b, N+, M0); and curative-intent surgical resection by laparoscopy or open approach | Emergency surgery (e.g., perforated colon); distant metastasis or synchronous colon cancer |
| Park *et al*. (2016)[45] | 93 | Pathologically confirmed primary colorectal cancer who underwent curative resection and clinically suspicious T4 disease | No recorded clinical T stage; recurrent colorectal cancer; distal metastasis; familial adenomatous polyposis; hereditary non-polyposis colorectal cancer; local resection; cT0-3 disease; nCRT |
| Chan *et al*. (2017) [46] | 52 | Tumours distal to the ileocecal valve until the rectosigmoid junction; pT4 staging | Emergency cases; direct invasion to adjacent organs; metastatic at presentation |
| Kang *et al*. (2017) [47] | 48 | pT4 colon cancer | Stage IV; hereditary non-polyposis colorectal cancer; robotic surgery |



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| Reference | N | Inclusion criteria | Exclusion criteria |
|---|---|---|---|
| Takahashi *et al*. (2017) [48] | 101 | Surgical T4b; both elective and emergency operations; distant metastases; T4b disease | Synchronous surgery for other diseases (primary gastric cancer, primary esophageal cancer, metastatic liver cancer, and pseudomyxoma peritonei) |
| Yang *et al*. (2018)[49] | 68 | Age of 18-75 years; proven T4 pathology; radical surgery (D3 lymph node dissection). | Low rectal cancer (peritoneal reflection as the boundary); preoperative neoadjuvant treatment; non-neoplastic deaths; and palliative resection |
| Leon *et al*. (2018)[33] | 130 | pT4N0-2M0 colon cancer; electively treated with curative intent | Not Mentioned |
| Yamanashi *et al*. (2018)[50] | 121 | Radical laparoscopic resection for pT4 colon and rectosigmoid cancer without transverse colon cancer, descending colon cancer, or rectosigmoid cancer requiring low anterior resection | Distant metastases; severe medical conditions; definite contiguous organ involvement on preoperative imaging, including cT4b tumor |
| Wang *et al*. (2018)[51] | 149 | Clinical T4 colon cancer colectomy | Not Mentioned |
| Lu *et al*. (2019)[52] | 24 | Nonmetastatic pathological T4 colon cancer; elective curative treatment; adenocarcinoma of the colon (histological confirmation was required at surgery); the absence of serious abdominal adhesions | pTis-pT3 colon cancer; metastatic disease; rectal cancer; emergency setting (acute bowel obstruction or perforation); severe medical illness; inflammatory bowel disease; familial polyposis; pregnancy; concurrent or previous malignant tumor |
| Park *et al*. (2019)[53] | 297 | Curative resection for pT4 primary colon cancer with proven adenocarcinoma. | pT1-3 colon cancers, palliative surgery, histology other than adenocarcinoma, hereditary cancer, synchronous colon cancer, or insufficient data |
| Aoki *et al*. (2019)[54] | 25 | pT4a/pT4b colon cancer | Recurrent tumor resection; concomitant cancers; palliative surgery; proctectomy |



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| Reference | N | Inclusion criteria | Exclusion criteria |
|---|---|---|---|
| Wasmann *et al*. (2019)[55] | 131 | pT4a/pT4b colon cancer who underwent surgery | Recurrent tumor resection, other concomitant cancers, palliative surgery, proctectomy |
| Miyo *et al*. (2020)[56] | 38 | Curative intent pT4N0-2M0 primary colon cancer resection | A macroscopic incomplete (R2) resection or with an inadequate pathological or surgical report |
| Nagata *et al*. (2020)[57] | 126 | Multivisceral resection for a locally advanced colon cancer that had invaded or adhered to adjacent organs; emergency surgery; a primary tumor resection with distant metastases; patients with bowel obstructions that were palliated with a colonic stent, ileus tube, and stoma before surgery | Rectal cancer or a recurrence of colorectal cancer |
| Park *et al*. (2020)[58] | 300 | Scheduled curative resection for pathological T4a colonic adenocarcinoma without distant or peritoneal metastases | Multiple colectomies for different primary tumor sites |
| El-Sharkasy *et al*. (2021)[59] | 7532 | Pathological T4 colon cancer who underwent curative surgery | Rectal cancer; T1–3 colon cancer; a histological diagnosis indicating cancer other than adenocarcinoma; palliative surgery; inflammatory bowel disease, or hereditary colon cancer |
| Parascandola *et al*. (2021)[60] | 876 | A diagnosis of adenocarcinoma of the colon, AJCC stage II or III, pathologic stage T4, age ≥18 years, surgical resection | Metastatic disease; rectosigmoid or rectal cancer; missing information on critical variables of interest (histologic diagnosis, stage, location of tumor, surgical approach, vital status, follow-up time, or chemotherapy use) |
| Sueda *et al*. (2021)[116] | 73 | pT4, stage II–III colon adenocarcinoma; identified using histology ICDO- 3 code 8140/3, who underwent partial or total colectomies | Data prior to 2010; missing or incomplete information; non-operative management; metastatic disease |



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Table 3. Clinical data of all patients (N=128) in cohort one

| Variables | |
|---|---|
| Age (years) [median±SD, (range)] | 62.5±13.8 (28-88) |
| Gender (female/male) | 56/72 |
| Body mass index (kg/m2) (mean±SD) | 23.5±4.2 |
| ASA (I/II/III/IV) | 4/51/72/1 |
| Previous abdominal surgery | |
| Open | 6 |
| Laparoscopy | 3 |
| Location of cancer, n (%) | |
| Cecum | 2(1.6%) |
| Ascending colon | 23 (18.0%) |
| Hepatic flexure | 2 (1.6%) |
| Transverse colon | 4 (3.1%) |
| Splenic flexure | 1 (0.8%) |
| Descending colon | 11 (8.6%) |
| Sigmoid colon | 41 (32.0%) |
| Rectosigmoid junction | 19 (14.8%) |
| Rectum | 25 (19.5%) |
| Clinically N staging | |
| N0 | 26 |
| N1 | 42 |
| N2 | 60 |
| Clinically M staging | |
| M0 | 90 (70.3%) |
| M1 | 38 (29.7%) |
| Preoperative chemoradiation therapy | 10 |
| Preoperative CEA level (ng/mL), median (range) | 23.6 (0.44-2167.3) |

BMI: body mass index; ASA: American society of Anesthesiology



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Table 4. Clinical characteristics between cT4a and cT4b LACRC undergoing minimally invasive surgery in cohort one

| | cT4a (n=22) | cT4b (n=68) | P-value |
|---|---|---|---|
| Age (years) [mean ± SD, (range)] | 66.2 ± 12.5 (40-83) | 63.1 ± 13.5(40-83) | 0.3282 |
| Gender (male/female), n | 14/8 | 39/29 | |
| BMI (kg/m2) (mean ± SD) | 23.7 ± 4.5 | 23.5 ± 3.7 | 0.8609 |
| ASA (I/II/III/IV), n | 0/9/13/0 | 4/24/39/1 | NA |
| Previous abdominal surgery, n | | | NA |
| Open | 1 | 5 | |
| Laparoscopy | 0 | 1 | |
| Location of cancer, n | | | 0.0500 |
| Cecum | 1 | 1 | |
| Ascending colon | 5 | 4 | |
| Hepatic flexure | 0 | 2 | |
| Transverse colon | 1 | 2 | |
| Splenic flexure | 1 | 0 | |
| Descending colon | 0 | 9 | |
| Sigmoid colon | 6 | 30 | |
| Rectosigmoid junction | 3 | 10 | |
| Rectum | 5 | 24 | |
| Preoperative chemoradiation therapy, n | 1 | 6 | 1.0000 |
| Preoperative CEA level (ng/mL), median (range) | 4.88 (0.92-1012.3) | 3.705 (0.44-348) | 0.4400 |

BMI: body mass index; ASA: American society of Anesthesiology; CEA: Carcinoembryonic Antigen



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Table 5. The clinicopathological data of all patients (N=128) in cohort one

| Variables | |
|---|---|
| Operative time (min) (median, range) | 309 (117-816) |
| Blood loss (ml) (median, range) | 175 (30-1200) |
| Diverting stoma [n(%)] | |
| Colostomy | 7 (5.5%) |
| Ileostomy | 23 (18.0%) |
| Conversion to open method | 10 (7.8%) |
| Radicality of surgery [n (%)] | |
| R0 | 83 (92.2%) |
| R1 | 6 (6.7%) |
| R2 | 1 (1.1%) |
| Tumor size (cm) (mean [range]) | 6.2 (2.2-18) |
| Harvested lymph nodes [median, IQR (25%-75%)] | 26 (17-34) |
| Differentiation[1] | |
| Well/moderately differentiated | 113 |
| Poorly/undifferentiated | 13 |
| pT stage | |
| T2 | 5 |
| T3 | 50 |
| T4a/ T4b | 47 / 26 |
| pN stage | |
| N0 | 37 |
| N1 | 45 |
| N2 | 46 |
| pM stage | |
| M1a | 24 |
| M1b | 6 |
| M1c | 8 |
| TNM stage | |
| II | 35 |
| III | 55 |
| IV | 38 |

[1] The grade of differentiation was not reported by pathologists in 2 patients because of status post neoadjuvant chemoradiation therapy



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Table 6. Surgical and pathological results between patient groups of cT4a and cT4b LACRC undergoing minimally invasive surgery in cohort one

| | cT4a (n=22) | cT4b (n=68) | P-value |
|---|---|---|---|
| Operative time, min | 271.2 ± 65.7 | 318.6 ± 71.3 | 0.0065 |
| Blood loss, mL | 121.8 ± 109.5 | 261.2 ± 263.9 | 0.0007 |
| Radicality, n | | | |
| R0 | 21 | 62 | 1.0000 |
| R1 | 1 | 5 | |
| R2 | 0 | 1 | |
| Conversion | 0 | 6 | 0.3295 |
| Clavien-Dindo Complication, n | | | 0.2450 |
| II | 3 | 12 | |
| III | 0 | 6 | |
| IV | 2 | 3 | |
| Time to flatus, d | 3.7 ± 1.1 | 4.6 ± 3.7 | 0.0942 |
| Time to resume a soft diet, d | 5.3 ± 2.0 | 8.1 ± 5.8 | 0.0007 |
| Postoperative length of stay, d | 11.0 ± 3.6 | 16.7 ± 13.5 | 0.0022 |
| Clinically N staging, n | | | 0.4943 |
| N0 | 6 | 20 | |
| N1 | 15 | 27 | |
| N2 | 16 | 44 | |
| Pathologically T staging, n | | | 0.0308 |
| T2 | 1 | 3 | |
| T3 | 5 | 37 | |
| T4 | 16 | 28 | |
| Pathologically N staging, n | | | 0.4429 |
| N0 | 7 | 28 | |
| N1 | 8 | 27 | |
| N2 | 7 | 13 | |



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Table 7. Characteristics of patients undergoing open conversion (n=6) in cohort one

| Case | Age/gender | Primary cancer site | Invaded organ | Radicality |
|---|---|---|---|---|
| 1 | 60M | Sigmoid | Urinary bladder | R0 |
| 2 | 69F | Sigmoid | Left adnexa (ovary) | R0 |
| 3 | 63M | Rectum | Prostate | R0 |
| 4 | 70M | Ascending colon | Liver | R0 |
| 5 | 62F | Sigmoid | Urinary bladder, left ureter | R1 |
| 6 | 53F | Sigmoid | Urinary bladder | R0 |



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Table 8 Literature review regarding the minimally invasive surgery for the treatment of cT4b LACRC requiring multivisceral resection

| Author (year) | Surgical type and case number | pT4, n (%) |
|---|---|---|
| | Invaded organs, n | |
| Kim *et al*. (2012)[77,81] | Laparoscopic surgery: 38 | 16 (42) |
| | Seminal vesicle: 7<br>Urinary bladder: 6<br>Small bowel: 4<br>Pararenal fat: 4<br>Pelvic lateral wall: 1<br>Peritoneum: 3<br>Duodenum: 1<br>Gallbladder: 1<br>Prostate gland: 3<br>Pelvic floor muscle: 3<br>Coccyx: 2 | Stomach: 1<br>Vagina: 1<br>Ovary: 1<br>Rectum: 1 |
| Nagasue *et al*. (2013) | Laparoscopic surgery: 60 | 34 (56.7) |
| | Abdominal wall: 7<br>Vagina: 7<br>Bladder: 6<br>Omentum 6<br>Levator ani muscle: 6<br>Ovary: 4<br>Peritoneum: 4<br>Seminal vesicle: 4<br>Gonadal vessels: 3<br>Small intestine: 3<br>Uterus: 3<br>Pararenal fat: 2<br>Appendix: 2<br>Other parts of colorectum: 2 | Coccyx: 1<br>Diaphragm: 1<br>Duodenum: 1<br>Liver: 1<br>Mesocolon: 1<br>Prostate: 1<br>Stomach: 1 |
| Takahashi *et al*. (2016)[48] | Laparoscopic surgery: 48 | 22 (45.8) |
| | Abdominal wall: 8<br>Intestine, mesenterium: 20<br>Retroperitoneum: 5<br>Uterus (partial resection), ovary: 5 | Bladder: 3 |
| Zhang *et al*. (2017)[78] | Laparoscopic surgery: 47<br>Hand-assisted laparoscopic surgery: 89 | Laparoscopic surgery: 31 (66.0)<br>Hand-assisted laparoscopic surgery: 59 (66.3) |
| | Laparoscopic surgery:<br>Abdominal wall: 11<br>Urinary bladder, 11<br>Ureter: 1<br>Kidney: 0<br>Ovary: 11<br>Liver wedge: 0<br>Gallbladder: 0<br>Small bowel: 13<br>Seminal vesicle and prostate: 1 | Hand-assisted laparoscopic surgery:<br>Abdominal wall: 25<br>Urinary bladder: 7<br>Ureter: 2<br>Kidney: 2<br>Ovary: 8<br>Liver wedge: 5<br>Gallbladder: 6<br>Small bowel: 34<br>Seminal vesicle and prostate: 2 |



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| Author (year) | Surgical type and case number | pT4, n (%) |
|---|---|---|
| | Invaded organs, n | |
| Miyake *et al.* (2017)[76] | Laparoscopic surgery: 39 | 10 (25.6) |
| | One resected organ | ≥2 resected organs: |
| | Abdominal wall: 12 | Abdominal wall and omentum: 1 |
| | Small intestine: 8 | Urinary bladder and urinary tract: 1 |
| | Urinary bladder: 5 | Urinary bladder and abdominal wall: 1 |
| | Colon: 4 | |
| | Mesentery: 3 | Retroperitoneum and abdominal wall and testicular artery: 1 |
| | Omentum: 1 | |
| | Ovary: 1 | Pancreas and duodenum:1 |
| Kumamoto *et al.* (2017) | Laparoscopic surgery: 118 | 54 (45.8) |
| | Peritoneum: 30 | Spermatic duct: 3 |
| | Small intestine: 17 | Duodenum: 2 |
| | Omentum: 17 | Ureter: 2 |
| | Bladder: 14 | Liver: 2 |
| | Other parts of colorectum: 13 | Gallbladder: 2 |
| | Ovary: 12 | Iliopsoas muscle: 2 |
| | Abdominal wall: 9 | Abdominal rectus muscle: 2 |
| | Uterus: 7 | Vagina: 1 |
| | Gonadal vessels: 5 | Diaphragm: 1 |
| | Pararenal fat: 5 | |
| Hino *et al.* (2017) | Robotic surgery: 31 | 9 (29.0) |
| | Vaginal wall: 12 | Coccyx: 2 |
| | Prostate: 10 | Uterus: 2 |
| | Seminal vesicle and/or vas deferens: 6 | Ovary and/or fallopian tube: 2 |
| Mukai *et al.* (2020)[79] | Laparoscopic surgery: 69 | 34 (49.3) |
| | Bladder: 17 | Seminal duct: 7 |
| | Abdominal wall or peritoneum: 18 | Other parts of colon or rectum: 4 |
| | Small intestine: 6 | Great omentum: 5 |
| | Gonadal vessels: 13 | Pararenal fascia: 4 |
| | Ovary: 11 | Vagina: 1 |
| | Uterus: 10 | Appendix: 1 |
| Miyo *et al.* (2020)[56] | Laparoscopic surgery: 38 | 11 (34.4) |
| | Abdominal wall: 17 | Ovary: 3 |
| | Retroperitoneum: 6 | Gonadal vessels: 1 |
| | Small intestine: 6 | Seminal vesicle: 1 |
| | Urinary bladder: 6 | Prostate:1 |
| | Omentum: 4 | Uterus: 2 |
| | Other parts of colorecum: 3 | Liver: 1 |
| Ishizaki *et al.* (2015) | Robotic surgery: 1 | 1 (100%) |
| | Urinary bladder: 1 | |
| Smith *et al.* (2020) | Robotic surgery: 5 | 1 (20%) |
| | Prostate:2 | Urinary bladder:1 |
| | Vaginal wall: 2 | Uterus:1 |



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Table 9. literature review of previous studies in PubMed regarding the laparoscopic surgery for cT4b LACRC

| Author (year) | R0 rate | Conversion rate | Overall complication | Mortality rate | Postoperative LOS,d |
|---|---|---|---|---|---|
| Kim *et al*. (2012)[77,81] | 68.4 | NA | 21.1 | 0 | 15.0 |
| Nagasue *et al*. (2013)[39] | 95.0 | 6.7 | 28.0 | 0 | 13.5 |
| Takahashi *et al*. (2016)[48] | 95.2 | 12.5 | 14.3 | 0 | 14.0 |
| Zhang *et al*. (2017)[78] | Lap: 95.7<br>HALS: 97.8 | Lap: 23.4<br>HALS: 2.2 | Lap: 25.5<br>HALS: 11.2 | 0, both | Lap: 8.0<br>HALS: 6.5 |
| Miyake *et al*. (2017)[76] | 100 | 28.2 | 28 | 0 | NA |
| Kumamoto *et al*. (2017)[73] | 94.9 | 6.8 | 17.8 | 0.8 | 11 |
| Hino *et al*. (2017)[80] | 90.3 | 0 | 35.5 | 0 | 8 |
| Mukai *et al*. (2020)[79] | 97.1 | 2.8 | 18.8 | 0 | 12 |
| Miyo *et al*. (2020)[56] | 84.4 | 5.3 | 10.5 | 0 | 12 |
| Ishizaki *et al*. (2015)[81] | 100 | 0 | 0 | 0 | NA |
| Smith *et al*. (2020)[82] | 100 | 0 | 60 | 0 | 17.4 |

Lap, laparoscopy; HALS, hand-assisted laparoscopic surgery; LOS, length of stay



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Table 10. Characteristics of cT4b LACRC patients with R1 or R2 resection in cohort one

| No. | Age/ gender | Primary cancer site | Surgery[1] | cT4b description | Radicality | Description of incomplete radicality |
|---|---|---|---|---|---|---|
| 1 | 76M | Ascending colon | L. right hemicolectomy | Colon serosa involvement | R2 | Superior mesenteric vein trunk involvement |
| 2 | 49M | Middle rectum | L. LAR | Right-sided pelvic wall involvement | R1 | Margin involved by carcinoma |
| 3 | 56F | Rectosigmoid junction | L.LAR | Rectal serosa involvement | R1 | Margin involved by carcinoma |
| 4 | 59M | Rectosigmoid junction | L.LAR | Rectal serosa involvement | R1 | Margin involved by carcinoma |
| 5 | 88M | Middle rectum | R. Hartmann procedure + partial bladder resection | Bladder wall invasion | R1 | Radical margin involved by carcinoma |
| 6 | 62F | Sigmoid colon | L.AR, conversion to open AR + partial bladder resection + ureter segmentectomy | Left ureter and bladder involvement | R1 | Margin involved by carcinoma |
| 7 | 63M | Low rectum | R.LAR[2] | Presacral involvement | R1 | Margin <1mm |

[1] L, laparoscopic; LAR, low anterior resection; AR, anterior resection; R, robotic

[2] The patient received preoperative neoadjuvant chemoradiation.



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Table 11. Clinical features of patients undergoing laparoscopic vs. robotic surgery in cohort two

| Variables | Laparoscopic group (N=32) | Robotic group (N=9) | *P*-value |
|---|---|---|---|
| Age (y) | 64.72 ± 10.89 | 69.00 ± 13.60 | 0.3299 |
| Gender (female/male), n | 7/25 | 2/7 | 1.0000 |
| BMI (kg/m$^2$) | 23.76 ± 3.46 | 24.68 ± 3.38 | 0.4810 |
| ASA class (I/II/III), n | 4/10/18 | 0/3/6 | 0.7413 |
| Previous abdominal surgery, n (%) | 8 (25.00) | 2 (22.22) | 1.0000 |
| CEA > 5.0 ng/mL, n (%) | 16 (50.0) | 4 (44.4) | 1.0000 |
| Primary tumor location, n (%) | | | 0.3010 |
| Sigmoid colon | 23 (71.88) | 5 (55.56) | |
| Rectosigmoid junction | 4 (12.50) | 0 (0.00) | |
| Rectum | 5 (15.63) | 4 (44.44) | |
| Neoadjuvant chemoradiation therapy, n (%) | 1 (3.13) | 1 (11.11) | 0.3951 |

ASA, the American Society of Anesthesiologists; BMI, body mass index; CEA, carcinoembryonic antigen

Continuous data were presented as mean ± standard deviation (SD)



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Table 12. Surgical and pathological features of patients undergoing laparoscopic vs. robotic surgery in cohort two

| | Laparoscopic group (N=32) | Robotic group (N=9) | *P*-value |
|---|---|---|---|
| Primary surgical procedure | | | 0.0577 |
| Anterior resection, n (%) | 17 (53.13) | 3 (33.33) | |
| Low anterior resection, n (%) | 15 (46.88) | 4 (44.44) | |
| Hartmann procedure, n (%) | 0 (0.00) | 2 (22.22) | |
| Operation time (min) | 353.24 ± 73.98 | 387.33 ± 200.62 | 0.6294 |
| Blood loss (mL) | 315.00 ± 304.32 | 171.11 ± 133.08 | 0.0516 |
| Conversion, n (%) | 4 (12.50) | 1 (11.11) | 1.0000 |
| No. of lymph nodes harvested | 27.16 ± 13.66 | 23.50 ± 9.71 | 0.4819 |
| Pathological TNM staging, n (%) | | | |
| pStage II: $T_{4a}N_0M_0$ | 11 (34.38) | 2 (22.22) | |
| $T_{4b}N_0M_0$ | 2 (5.71) | 1 (11.11) | |
| pStage III: $T_{4a}N_{1\text{-}2}M_0$ | 11 (34.38) | 2 (22.22) | |
| $T_{4b}N_{1\text{-}2}M_0$ | 5 (15.63) | 1 (11.11) | |
| pStage IV: $M_1$, any T, any N | 3 (9.38) | 3 (33.33) | |
| Radicality of CRM, n (%) | | | 0.0968 |
| R0 | 28 (87.50) | 5 (55.56) | |
| R1 | 4 (12.50) | 4 (44.44) | |
| Flatus passage (h) | 4.84 ± 4.03 | 4.09 ± 2.10 | 0.6170 |
| Postoperative length of stay (d) | 18.88 ± 16.30 | 19.78 ± 11.76 | 0.8779 |
| Postoperative complications, n (%) | | | |
| Bowel anastomotic leakage | 3 (9.38) | 0 (0.00) | 1.000 |
| Urinary leakage | 1 (3.13) | 0 (0.00) | 1.000 |
| Intra-abdominal abscess | 1 (3.13) | 1 (11.11) | 0.3951 |
| Ileus | 1 (3.13) | 1 (11.11) | 0.3951 |
| Urinary retention | 2 (6.25) | 0 (0.00) | 1.000 |
| Clavien-Dindo complication classification (≥II), n (%) | | | 0.1398 |
| II | 9 (28.13) | 3 (3.33) | |
| III | 2 (6.26) | 2 (2.22) | |
| IV | 1 (3.13) | 0 (0.00) | |

Continuous data were presented as mean ± standard deviation (SD)

CRM: circumferential resection margin



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Table 13. Multivariate Cox regression for 5-year disease-free survival rate in cohort two

| Factor | Hazard ratio (95% confident interval) | P-value |
|---|---|---|
| Age (years) | 1.037 (0.933–1.151) | 0.5023 |
| Gender (male vs. female) | 0.261 (0.024–2.849) | 0.2703 |
| Pathological staging (stage III vs stage II) | 0.801 (0.109–5.897) | 0.8278 |
| Surgical method (Robotic vs. laparoscopic method) | 1.187 (0.095–14.763) | 0.8940 |
| Radicality (R1 vs. R0) | 21.386 (1.991–229.723) | 0.0115 |
| Lymphovascular invasion (Yes vs. No) | 7.777 (0.889–68.029) | 0.0638 |
| Perineural invasion (Yes vs. No) | 0.630 (0.041–9.753) | 0.7410 |



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# APPENDIX

1. **<u>Yu-Tso Liao</u>**, John Huang, Tzu-Chun Chen, Ji-Shiang Hung, Jin-Tung Liang. Technical Feasibility of Robotic versus Laparoscopic Surgery for Locally Advanced Colorectal Cancer Invading the Urinary Bladder. Tech Coloproctol, 2022 Nov;26(11):905-914 (IF: 3.699, 50/212, Q1 SURGERY)
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