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VU NGOC SON

**A STUDY OF LAPAROSCOPIC SURGERY FOR THE
TREATMENT OF MIDDLE AND LOWER RECTAL
ADENOCARCINOMA AFTER LONG-COURSE
PREOPERATIVE CHEMORADIOOTHERAPY**

Speciality : Surgery
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INTRODUCTION

Rectal cancer (RC) is a relatively common malignancy worldwide as well as in Vietnam, with an increasing incidence in recent years.

At present, preoperative long-course preoperative chemoradiotherapy (LC-CRT) is recommended as the standard treatment for locally advanced middle and low RC. The role of preoperative LC-CRT is to reduce tumor size, limit tumor invasion, increase the rate of radical resection and sphincter preservation, improve the complete response rate, and reduce local recurrence. The three most commonly used regimens today are short-course radiotherapy, long-course LC-CRT, and total neoadjuvant therapy.

Studies on long-course LC-CRT combined with laparoscopic rectal resection have shown response rates ranging from 53.1% to 71.7%, with anal preservation rates from 68% to 76%. Kairevičė L. reported a 5-year postoperative survival rate of 65%–81% in the long-course LC-CRT group. Studies have also demonstrated the effects of preoperative LC-CRT on RC surgery, such as peritumoral inflammatory adhesions, increased risk of anastomotic leakage, and perineal wound infection. In Vietnam, several studies have addressed preoperative LC-CRT in RC; however, they have mainly reported preliminary outcomes and have not comprehensively evaluated the role, advantages, and disadvantages of LC-CRT, as well as laparoscopic surgical outcomes and long-term follow-up results. For these reasons, we conducted the study entitled “A Study on Laparoscopic Surgery for Middle and Low Rectal Adenocarcinoma Following LC-CRT” with the following two objectives:

Objective 1: To describe selected pathological characteristics and the effectiveness of LC-CRT in patients with middle and low rectal adenocarcinoma.

Objective 2: To evaluate the outcomes of laparoscopic surgery for middle and low rectal adenocarcinoma following LC-CRT.

NEW CONTRIBUTIONS OF THE THESIS

Regarding the pathological characteristics and effectiveness of LC-CRT: the most common symptom was bloody stool. Pre-treatment MRI showed cT3 invasion in 71.4% of patients. CEA was elevated in 40.48% of patients.

Before LC-CRT, 95.24% of patients were classified as stage III. LC-CRT was a safe treatment, with a regimen completion rate of 98.81% and low rates of toxicity and adverse effects. Post-LC-CRT MRI showed that most patients achieved mrTRG 3 response (46.43%), while 14.88% achieved complete response, corresponding to mrTRG 1. Histopathological results showed a complete response rate of 22.02% (TRG 1). Disease downstaging was observed, with 18.5% of patients classified as stage 0, 38.10% as stage I, 29.17% as stage II, while stage III decreased to 14.29%.

Regarding surgical outcomes:

Intraoperative outcomes: Tumor location was evenly distributed between the middle third and lower third of the rectum. Radiation-induced inflammatory adhesions were observed in 42.86% of patients; only 23.21% underwent abdominoperineal resection. The intraoperative complication rate was low (5.36%), and 4 cases (2.38%) required conversion to open surgery.

Early outcomes: Early complications were mainly Clavien–Dindo grade I–II; 3.66% of patients required reoperation (grade IIb). No severe complications (grade IV–V) were recorded. There was no intraoperative or postoperative mortality.

Long-term outcomes: Laparoscopic surgery demonstrated favorable oncological outcomes, with a local recurrence and/or distant metastasis rate of 17.6%. The 5-year overall survival and disease-free survival rates were 82.7% and 80.7%, respectively. Prognostic factors for recurrence/distant metastasis and overall survival included pathological response after LC-CRT, specimen quality, and post-LC-CRT CEA level. Poor pathological response according to the Mandard classification, particularly TRG 4 and TRG 5, increased the risk of recurrence/distant metastasis and death.

STRUCTURE OF THE THESIS

The thesis consists of 150 pages, including 2 pages of introduction, 37 pages of literature review, 27 pages of subjects and methods, 30 pages of results, 51 pages of discussion, 2 pages of conclusions, and 1 page of recommendations. The thesis includes 2 published research works, 46 tables, 15 charts, and 17 figures. There are 182 references, including 09 Vietnamese references and 173 foreign-language references.

CHAPTER 1: LITERATURE REVIEW

1.1. Rectal cancer

1.1.1. Epidemiology

1.1.2. Surgical Anatomy of the Rectum

1.1.2.1. External Morphology

1.1.2.2. Blood Supply and Lymphatic Drainage

1.1.2.3. Mesorectum

1.1.2.4. Pelvic Fascial Planes

1.1.3. Diagnosis

1.1.3.1. Clinical Assessment

1.1.3.2. Paraclinical Investigations

Colonoscopy and rectoscopy with biopsy

Pelvic MRI for evaluation of tumor location, local invasion, and lymph node metastasis

Chest and abdominal CT Scan: assessment of distant metastasis

Disease staging: according to the AJCC classification

1.1.4. Treatment of Middle and Low RC

1.1.4.1. Preoperative Neoadjuvant Therapy

1.1.4.2. Surgery

Endoscopic tumor/polyp resection or local excision

Miles' operation

Sphincter-preserving procedures: Hartmann's procedure, anterior resection, low anterior resection, intersphincteric resection, and total mesorectal excision

1.2. Studies on LC-CRT for RC

1.2.1. History

1.2.2. Scientific Basis

Chemotherapeutic agents used in combination with neoadjuvant radiotherapy increase tumor radiosensitivity, have low toxicity, and, because they can be administered orally, are simple and convenient to use.

1.2.3. Indications

According to ESMO and NCCN, LC-CRT is indicated for locally advanced middle and low rectal tumors, particularly those classified as T3c/d,

with a positive circumferential resection margin or extramural vascular invasion on pre-treatment MRI.

1.2.4. Treatment Regimen

Long-course LC-CRT consists of 1.8-2 Gy per fraction over 5-5.5 weeks, with a total dose of 45-50.4 Gy combined with 5-FU-based chemotherapy, followed by an interval of 5 to 12 weeks before surgery.

1.2.5. Methods for Evaluating Response After Long-Course LC-CRT

1.2.5.1. Primary Objectives

1.2.5.2. Important Definitions

1.2.5.3. Clinical Assessment

1.2.5.4. Magnetic Resonance Imaging: MRI plays an important role in local restaging of RC after preoperative LC-CRT.

1.2.5.5. Changes in CEA Marker Levels

1.2.5.6. Histopathological Response Assessment

Response is classified according to the Tumor Regression Grade scale, which reflects the degree of tumor regression.

1.2.6. Role of the Multidisciplinary Tumor Board

1.2.7. Outcomes of LC-CRT for RC

The CAO/ARO/AIO-94 trial confirmed the important role of LC-CRT before surgery. In the NSABP R-03 trial, the 5-year DFS rate among patients receiving LC-CRT was 64.7%; the 5-year OS rate was 74.5%, and the pathological complete response rate was 15%. In Vietnam, Truong Thu Hien reported a post-treatment response rate of 83.4%. Postoperative histopathology showed a pathological complete response rate of 25%, tumor downstaging in 85.4%, and nodal downstaging in 91.7%.

1.3. Outcomes of Laparoscopic Surgery for Middle and Low RC Following LC-CRT

1.3.1. Worldwide: The COREAN trial showed that the conversion rate to open surgery in the laparoscopic surgery group was 1.2%, with a low positive circumferential resection margin rate of 3%; the 3-year DFS rate was 79.2% in the laparoscopic surgery group. Laparoscopic surgery for RC has been widely adopted because postoperative mortality and morbidity remain within acceptable limits.

1.3.2. In Vietnam: In general, domestic data show that laparoscopic surgery after LC-CRT is associated with a low conversion rate, minimal blood loss, an acceptable rate of anastomotic leakage, and no or very low postoperative mortality, while also providing favorable mid- to long-term OS and DFS outcomes.

CHAPTER 2: SUBJECTS AND METHODS

2.1. Study Subjects

Patients diagnosed with stage II-III middle and low RC who underwent LC-CRT combined with radical laparoscopic surgery at the 108 Military Central Hospital from August 2018 to August 2023, with long-term follow-up until May 2025.

2.1.1. Inclusion Criteria

Patients with a confirmed diagnosis of stage II or III middle and low RC before treatment; patients who received LC-CRT followed by radical laparoscopic surgery, including both patients with successful laparoscopic surgery and those converted to open surgery due to technical difficulties or intraoperative complications; ASA score < 3; complete medical records; and patients who agreed to participate in the study.

2.1.2. Exclusion Criteria

Patients who did not fully complete the LC-CRT regimen; patients with recurrent RC; patients with a history of anorectal surgery causing injury and loss of anal sphincter continence; and patients with contraindications to laparoscopic surgery.

2.2. Research Methods

2.2.1. Study Design

A retrospective and prospective descriptive case-series study with longitudinal follow-up and no control group.

2.2.2. Sample Size

The sample size was calculated according to the formula. A total of 168 eligible patients were included in the study to evaluate pathological characteristics, the effectiveness of LC-CRT, and intraoperative outcomes.

Four patients required conversion to open surgery; therefore, 164 patients were evaluated for laparoscopic surgical outcomes, including early postoperative outcomes and long-term follow-up results.

2.2.3. Data Collection Method

2.2.4. Treatment Protocol for Patients with RC in the Study

2.2.4.1. Diagnosis on Admission

2.2.4.2. MRI Acquisition and Assessment Protocol in the Study

2.2.4.3. LC-CRT Protocol

The radiotherapy regimen consisted of a total dose of 45-50.4 Gy, delivered in 25-28 fractions, combined with Capecitabine chemotherapy.

2.2.4.4. Preoperative Patient Preparation

2.2.4.5. Preparation of Surgical Instruments and Equipment

2.2.4.6. Indications for Selection of Surgical Techniques

2.2.4.7. Surgical Steps

2.2.4.8. Specimen Preparation and Assessment

2.2.4.9. Postoperative Monitoring and Care

2.2.5. Study Variables

2.2.5.1. Pathological Characteristics and Effectiveness of LC-CRT

- Pathological characteristics before LC-CRT: age, sex, BMI, family history of cancer, time from disease detection, functional symptoms, MRI findings before LC-CRT, degree of cellular differentiation, CEA level before LC-CRT, and disease staging before LC-CRT according to the AJCC 8th edition.
- Evaluation of the effectiveness of LC-CRT: clinical course during LC-CRT, interval after LC-CRT, toxicities and adverse effects, clinical response assessment, changes in functional symptoms, MRI response after LC-CRT, changes in CEA level, and postoperative pathological response assessment according to the Mandard classification.

2.2.5.2. Evaluation of Surgical Outcomes

- Intraoperative outcomes: assessment of lesions, distant metastasis, radiation-induced adhesions, surgical method, technical characteristics including number of trocars, splenic flexure mobilization, lateral pelvic lymph node dissection, and method of anastomosis; intraoperative complications, conversion to open surgery, operative time, and blood loss.
- Early outcomes: duration of postoperative pain, postoperative hospital stay, early complications, and mortality.
- Long-term outcomes: follow-up and patient re-examination at 1 year, 2 years, 3 years, and subsequent postoperative time points, as well as at the end

of the study in May 2025. Recorded variables included long-term follow-up duration, late complications, evaluation of anal sphincter function according to the Wexner score, assessment of local recurrence and distant metastasis, evaluation of overall survival (OS), disease-free survival (DFS), and univariate and multivariate analyses of factors associated with OS and DFS.

2.2.6. Data Processing

2.2.7. Research Ethics of the Study

CHAPTER 3: RESEARCH RESULTS

3.1. Pathological Characteristics and Effectiveness of LC-CRT

3.1.1. Pathological Characteristics Before LC-CRT

- The mean age was 62.0 years. Patients aged ≥ 60 years accounted for 66.07%. Males accounted for 69.64%. The mean BMI was 22.0 kg/m², and 14.29% of patients were overweight or obese.

- A family history of cancer was recorded in 10.7% of patients.

- Bloody stool was the most common symptom, accounting for 92.86%, followed by weight loss in 55.36% and tenesmus in 46.43%.

- The mean time from disease detection was 5.14 ± 6.75 months.

Table 3.4. Pre-treatment MRI characteristics of lesions (n = 168)

Pre-treatment MRI characteristics		Number	Percentage
Tumor size (cm)	Mean	5.6 ± 2.2	
Tumor invasion	cT1	0	0
	cT2	7	4.2
	cT3	120	71.4
	cT4	41	24.4
Peritumoral lymph nodes	Present	160	95.24
Number of lymph nodes	Mean	5.1 ± 2.4	

Comment: The most common invasion levels were cT3 (71.4%) and cT4 (24.4%). The rate of peritumoral lymph nodes was 95.24%.

- Most patients had moderately differentiated tumors, accounting for 89.88%.

- The mean CEA level was 9.9 ng/mL. Pre-treatment CEA elevation was observed in 40.48% of patients.

- A total of 95.24% of patients were diagnosed as stage III before LC-CRT.

3.1.2. Evaluation of the Effectiveness of LC-CRT

3.1.2.1. Characteristics of LC-CRT

- A total of 98.81% of patients completed LC-CRT according to the protocol; 2 patients (1.19%) required temporary surgery and subsequently continued LC-CRT. The mean interval from completion of LC-CRT to surgery was 6.6 weeks, mainly from 6 to 8 weeks, accounting for 91.07%.

- Regarding toxicity and adverse effects, the most common events were grade 1 radiation dermatitis (10.1%) and grade 2 radiation dermatitis (7.8%). Grade 2 fatigue accounted for 3%, while grade 2 anemia and grade 2 leukopenia each occurred in less than 2% of patients. No grade 4–5 toxicity was recorded.

3.1.2.2. Clinical Response Assessment

- Changes in functional symptoms: after LC-CRT, 41.1% of patients had complete resolution of symptoms, while 3.0% showed no improvement.

Table 3.10. MRI characteristics of lesions after LC-CRT (n = 168)

MRI characteristics after LC-CRT		Number	Percentage
Lesion visible on MRI		156	92.86
Tumor invasion	ycT0	12	7.14
	ycT1	13	7.74
	ycT2	33	19.64
	ycT3	102	60.72
	ycT4	8	4.76
Peritumoral lymph nodes	Present	119	70.83
	Mean number of lymph nodes	3.1 ± 2.4	

Comment: Lesions remained visible in 92.86% of patients. The most common invasion level was ycT3, accounting for 60.72%.

Table 3.11. Changes in tumor size on MRI before and after LC-CRT

Tumor size on MRI		Before LC-CRT	After LC-CRT	p
Tumor size	Mean	5.6 ± 2.2	4.21 ± 2.0	< 0.001
	Min - Max	1.8 – 14	0.6 – 12.6	Wilcoxon test

Comment: The mean tumor size on MRI decreased from 5.6 cm before LC-CRT to 4.2 cm after LC-CRT ($p < 0.001$).

Table 3.12. Changes in the number of lymph nodes on MRI before and after LC-CRT

Lymph node characteristics on MRI		Before LC-CRT	After LC-CRT	p
number of lymph nodes	Mean	5.1 ± 2.4	3.1 ± 2.5	< 0.001
	Min - Max	0 – 20	0 - 14	Wilcoxon test

Comment: The mean number of lymph nodes on MRI decreased from 5.1 before LC-CRT to 3.1 after LC-CRT ($p < 0.001$).

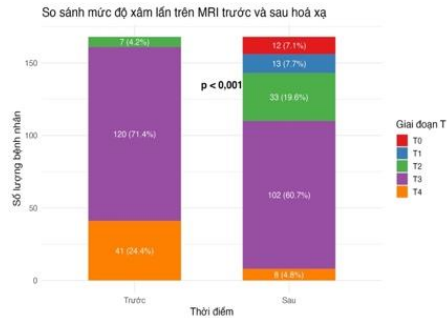


Figure 3.2. Comparison of tumor invasion on MRI before and after LC-CRT

Comment: Before treatment, most patients were classified as T3 (71.4%) and T4 (24.4%). After LC-CRT, these rates decreased to 60.7% for T3 and 4.8% for T4, respectively.

Table 3.13. MRI-based assessment of tumor response after LC-CRT

MRI response level after LC-CRT	Number	Percentage
mrTRG 1 - Complete response	25	14.88
mrTRG 2 - Good response	36	21.43
mrTRG 3 - Moderate response	78	46.43
mrTRG 4 - Poor response	11	6.55
mrTRG 5 - No response	18	10.71

Comment: Most patients (46.43%) achieved a moderate response (mrTRG 3). Complete response on MRI after LC-CRT was observed in 14.88%.

- The diagnostic agreement between mrTRG classification and Mandard TRG classification was low, with a Kappa coefficient of 0.2496 and $p < 0.001$. The Spearman rho correlation coefficient was 0.528 with $p < 0.001$, reflecting a moderate positive correlation between the two classification systems.

3.1.2.3. Characteristics of CEA After Treatment

- After LC-CRT, only 8.33% of patients had CEA > 5 ng/mL, a significant reduction compared with before LC-CRT (40.48%) ($p < 0.001$). The mean post-LC-CRT CEA level (3.49 ng/mL) was lower than the pre-LC-CRT level (9.9 ng/mL), with $p < 0.001$.

3.1.2.4. Evaluation of Pathological Response After Surgery

- Lesion characteristics: The mesorectal specimen was assessed as complete in 72.62% of cases. The main lesion morphology was exophytic tumor (68.05%); no visible lesion was observed in 1.19%, and only an area of mucosal irregularity was seen in 19.05%.

- Microscopic characteristics: No residual tumor cells were found in 37 cases (22.02%). The predominant invasion levels were ypT3 (34.52%) and ypT2 (33.33%).

- Lymph node metastasis characteristics: The rate of mesorectal lymph node metastasis was 11.31%, and left lateral pelvic lymph node metastasis was 16.0%. No patient had right lateral pelvic lymph node metastasis.

- Assessment of resection margins: The mean distance from the lower tumor border to the distal resection margin was 2.9 ± 1.4 cm. No residual tumor cells were detected at the proximal or distal resection margins in 100% of cases. One patient had tumor cells at the circumferential resection margin.

- Postoperative pathological response assessment: Most patients achieved partial response (TRG 3), accounting for 50.0%. The complete response rate (TRG 1) was 22.02%. The rates of TRG 2, TRG 4, and TRG 5 were 17.26%, 8.33%, and 2.38%, respectively.

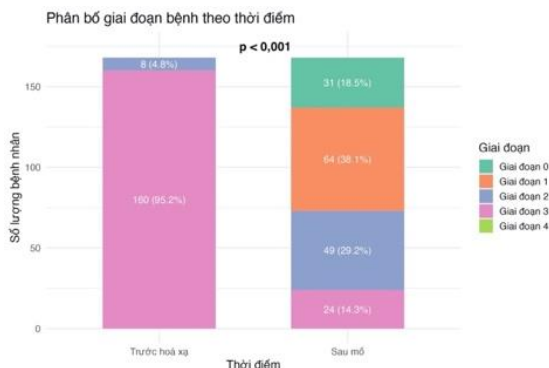


Figure 3.3. Comparison of disease stage before LC-CRT and after surgery

Comment: There was a significant change in disease stage distribution before LC-CRT and after surgery ($p < 0.001$). Before LC-CRT, most patients were stage III (95.2%). After surgery, the proportion of stage III patients decreased to 14.3%, and 18.5% were classified as stage 0.

3.2. Evaluation of Surgical Outcomes

3.2.1. Intraoperative Outcomes

- Intraoperative lesions: Tumor location was evenly distributed between the middle third (50.60%) and lower third (49.40%) of the rectum. Radiation-induced adhesions were observed in 42.86% of patients.

Table 3.25. Surgical methods (n = 168)

Surgical method	Number	Percentage
Total mesorectal excision	81	48.21
Intersphincteric resection	42	25.00
Miles' operation	39	23.21
Hartmann's procedure	6	3.57

Comment: TME was the most frequently performed procedure, accounting for 48.21%. Hartmann's procedure was performed in 6 patients (3.57%).

- Association between surgical method and tumor location: In the middle-third rectal tumor group, the main procedure was total mesorectal excision, accounting for 84.88%. In the lower-third rectal tumor group,

52.44% underwent sphincter-preserving surgery and 46.99% underwent Miles' operation ($p < 0.001$).

- Some technical characteristics: A five-trocar approach was used in 63.69% of patients. Splenic flexure mobilization was performed in 43.45%. Lateral pelvic lymph node dissection was performed in 14.88% of patients, including bilateral lateral pelvic lymph node dissection in 8.93%. Anastomosis was mainly performed using a stapling technique, accounting for 72.36%. Placement of an anal tube was the most commonly used method for anastomotic protection, accounting for 56.10%.

Table 3.28. Intraoperative complications (n = 168)

Intraoperative complications	Number	Percentage
Presacral venous plexus injury	3	1.79
Left ureteral injury	1	0.60
Left obturator nerve injury	1	0.60
Splenic parenchymal injury	1	0.60
Left iliac vein tear	1	0.60
Bleeding from the dissection plane due to tumor invasion	2	1.19

Comment: The intraoperative complication rate was 5.36%.

- Four patients (2.38%) required conversion to open surgery.
- The mean operative time was 133.4 ± 33.7 minutes (range: 70–300).
- The mean blood loss was 71.1 ± 107.8 mL (range: 10–1000 mL).

3.2.2. Early Outcomes (n = 164)

- The mean postoperative pain duration was 2.71 ± 1.0 days.
- The mean postoperative hospital stay was 10.9 ± 5.5 days.

Table 3.32. Early complications (n = 164)

Early complications	Number	Percentage
Bleeding	2	1.22
Surgical site infection	6	3.66
Anastomotic leakage (n = 121)*	6	4.96
Early bowel obstruction	2	1.22
Urinary retention	11	6.71
Ureteral fistula	2	1.22

Urethral fistula	1	0.60
Chylous fistula	1	0.60
Intraoperative or postoperative mortality	0	0

*Calculated among 121 patients with an anastomosis.

Comment: The most common early complications were urinary retention (6.71%) and anastomotic leakage (4.96%). No intraoperative or postoperative death was recorded.

- Early complications according to the Clavien–Dindo classification were mainly grade I–II, accounting for 11.59%. Six cases (3.66%) required reoperation (grade IIIb). No severe complications (grade IV–V) were recorded.

3.2.3. Long-Term Outcomes (n = 164)

- The mean long-term follow-up duration was 48.8 ± 15.3 months (range: 5–80).

- Anal sphincter function: The mean Wexner score gradually decreased over time in both surgical groups; however, the ISR group consistently had a higher mean score than the total mesorectal excision group, reflecting poorer sphincter continence function.

Table 3.34. Late complications

Late complications	Number	Percentage
Late anastomotic leakage ($n=121$)**	4	3.31
Anastomotic stricture ($n=121$)**	7	5.79
Adhesive partial bowel obstruction ($n=164$)*	3	1.83
Bladder atony ($n=164$)*	1	0.60
Left ureteral stricture ($n=164$)*	1	0.60
Rectourethral fistula ($n=164$)*	1	0.60
Parastomal hernia ($n=43$)***	4	9.30
Necrotizing inflammation of the anastomosis ($n=121$)**	1	0.83

*Number of remaining patients. **Number of patients with an anastomosis. ***Number of patients with a stoma.

Comment: Common late complications included parastomal hernia (9.3%), anastomotic stricture (5.79%), and late anastomotic leakage (3.31%).

- The rate of local recurrence and/or distant metastasis was 17.6%. The mean time to recurrence/metastasis was 23.9 ± 12.47 months, with a maximum of 50 months and a minimum of 5 months.

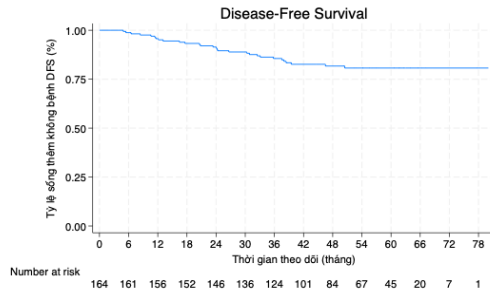


Figure 3.8. Kaplan–Meier analysis of disease-free survival

Comment: The 1-year, 3-year, and 5-year postoperative disease-free survival rates were 95.7%, 85.6%, and 80.7%, respectively.

- Univariate analysis showed that factors associated with the risk of recurrence/distant metastasis included male sex, poor MRI response after LC-CRT classified as mrTRG 4–5, post-LC-CRT CEA > 5 ng/mL, and poorer pathological response, with TRG 4 and TRG 5 increasing the risk of recurrence/distant metastasis.

- In multivariate analysis, post-LC-CRT CEA > 5 ng/mL, TRG 4 and TRG 5, and nearly complete specimen quality were also independent prognostic factors that increased the risk of recurrence/distant metastasis.

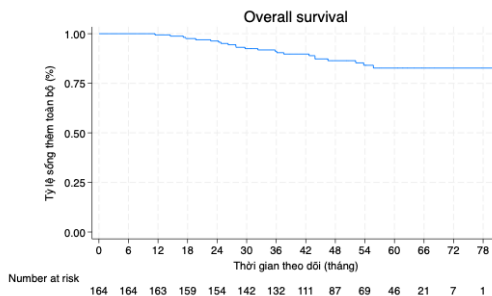


Figure 3.12. Kaplan–Meier analysis of overall survival (n = 164)

Comment: The 1-year, 3-year, and 5-year postoperative overall survival rates were 99.4%, 91.1%, and 82.7%, respectively.

- Univariate analysis showed that an interval of less than 6 weeks from the completion of LC-CRT to surgery, poor MRI response after LC-CRT classified as mrTRG 4–5, post-LC-CRT CEA > 5 ng/mL, and poor pathological response (TRG 4–5) were significantly associated with reduced OS.

- In multivariate analysis, independent prognostic factors included an interval of less than 6 weeks from LC-CRT to surgery and post-LC-CRT CEA > 5 ng/mL. Poor pathological response (TRG 4–5) was among the strongest independent prognostic factors, indicating a higher risk of mortality.

CHAPTER 4: DISCUSSION

4.1. Pathological Characteristics and Effectiveness of LC-CRT

4.1.1. Pathological Characteristics Before LC-CRT

In this study, the mean age of the patients was 62.0 years; patients older than 60 years accounted for 66.07%, and males accounted for 69.64%. These characteristics are consistent with the epidemiology of RC, which commonly occurs in elderly patients and shows a predominance in males. The mean body mass index was $22.0 \pm 2.91 \text{ kg/m}^2$, with most patients falling within the normal BMI range, indicating that the general physical condition of the study population was relatively favorable for multimodal treatment.

A family history of cancer was recorded in 10.7% of patients, among whom RC was the most common. The most frequent clinical symptom was bloody stool, accounting for 92.86%, followed by weight loss in 55.36% and tenesmus in 46.43%. These are typical manifestations of middle and low RC; however, they often appear when the disease has already progressed locally.

On pre-treatment MRI, most tumors were classified as cT3 and cT4, accounting for 71.4% and 24.4%, respectively; peritumoral lymph nodes were detected in 95.24% of patients. All patients were diagnosed with adenocarcinoma by biopsy, predominantly moderately differentiated adenocarcinoma, with a rate of 89.88%. The mean pre-treatment CEA level was $9.9 \pm 30.5 \text{ ng/mL}$, and CEA elevation was observed in 40.48% of patients. Notably, 95.24% of patients were diagnosed as stage III before LC-CRT, reflecting the fact that most patients were admitted at a locally

advanced stage, in accordance with the indication for LC-CRT according to current recommendations.

4.1.2. Evaluation of the Effectiveness of LC-CRT

4.1.2.1. Characteristics of LC-CRT

The completion rate of LC-CRT in this study reached 98.81%; only 1.19% of patients required a temporary stoma before continuing treatment. This result indicates that the regimen was safely and feasibly implemented, with a high level of treatment compliance. Most patients underwent surgery within 6–8 weeks after LC-CRT, accounting for 91.07%, which is consistent with recommendations regarding the timing of surgery after neoadjuvant treatment. Toxicities and adverse effects during LC-CRT were mainly mild to moderate. The most common toxicity was grade 1–2 radiation dermatitis; only a few cases of grade 3 toxicity were observed, and no grade 4–5 toxicity was recorded. All adverse effects were controlled by medical treatment and did not significantly affect the ability to complete the regimen.

4.1.2.2. Evaluation of Clinical Response

After LC-CRT, 41.1% of patients had complete resolution of functional symptoms, 55.9% showed near-complete improvement, and only 3.0% had no improvement. This confirms the role of long-course LC-CRT in symptom control, particularly for rectal bleeding, tenesmus, and anal pain.

On post-treatment MRI, residual lesions were still visible in 92.86% of patients; however, the mean tumor size decreased from 5.6 cm to 4.2 cm, corresponding to an approximate reduction of 25%. The mean number of lymph nodes also decreased from 5.1 to 3.1 nodes. Regarding tumor invasion, the proportions of ycT3 and ycT4 decreased compared with those before treatment, while cases of ycT0 and ycT1 appeared, demonstrating the downstaging effect of LC-CRT.

Response assessment according to the MERCURY criteria showed that most patients achieved mrTRG 3, accounting for 46.43%; mrTRG 2 accounted for 21.43%, and mrTRG 1 accounted for 14.88%. These findings indicate that post-LC-CRT MRI is valuable for response stratification and surgical planning. However, the correlation between mrTRG and histopathological response was limited; therefore, MRI cannot completely replace postoperative pathological assessment.

4.1.2.3. Evaluation of Response Based on Changes in CEA Levels

After LC-CRT, the proportion of patients with CEA > 5 ng/mL decreased from 40.48% to 8.33%; the mean CEA level decreased from 9.9 to 3.49 ng/mL, with a statistically significant difference. This suggests that CEA has certain value in monitoring treatment response. Nevertheless, CEA is not an absolute marker, because some patients may have normal CEA levels from the outset, or may still harbor microscopic disease despite a decline in CEA. Therefore, CEA should be combined with MRI, endoscopy, and pathological assessment to comprehensively evaluate response after LC-CRT.

4.1.2.4. Evaluation of Pathological Response After Surgery

The quality of the total mesorectal excision specimen was assessed as complete in 72.62%, nearly complete in 22.62%, and incomplete in 4.76%. This is an important result, reflecting the quality of TME surgery in the context of a post-LC-CRT operative field, which is often characterized by fibrosis, edema, and more extensive adhesions.

On postoperative specimens, residual tumor lesions were observed in 92.86% of cases, mainly presenting as exophytic tumors. The mean lesion size was 2.18 ± 1.5 cm. Regarding the depth of invasion, ypT3 accounted for 34.52%, ypT2 for 33.33%, ypT1 for 7.14%, and ypT4 for 2.98%. Notably, 37 patients achieved pCR in the specimen, accounting for 22.02%.

The mean number of harvested lymph nodes was 6.1. The rate of mesorectal lymph node metastasis was 11.31%; left lateral pelvic lymph node metastasis was recorded in several cases, whereas no right lateral pelvic lymph node metastasis was observed. This demonstrates that lymph node assessment and dissection remain important even in patients with a good response of the primary tumor.

According to the TRG classification, complete response accounted for 22.02%, near-complete response for 17.26%, partial response for 50.0%, poor response for 8.33%, and no response for 2.38%. The postoperative disease stage distribution changed markedly compared with the pre-LC-CRT stage: stage I accounted for 38.10%, stage II for 29.17%, stage III decreased to 14.29%, and no patient was classified as stage IV. This change demonstrates the downstaging effect of LC-CRT. It should be noted that among the 37 patients with no residual tumor cells at the primary tumor site,

only 31 patients achieved complete response in terms of disease stage, because some cases still had lymph node metastasis. Therefore, radical surgery and lymph node dissection according to oncological principles remain necessary, even in patients with complete local response.

4.2. Evaluation of Surgical Outcomes

4.2.1. Intraoperative Outcomes

Tumor location was relatively evenly distributed between the middle third and lower third of the rectum, accounting for 50.60% and 49.40%, respectively. The main surgical approach was sphincter-preserving surgery, accounting for 73.21%, including laparoscopic TME in 48.21% and intersphincteric resection in 25.00%. Abdominoperineal resection accounted for 23.21%, and Hartmann's procedure for 3.57%. Tumor location was closely associated with the surgical method; tumors in the middle third of the rectum were mainly treated with sphincter-preserving TME, whereas tumors in the lower third had a higher rate of abdominoperineal resection because of the requirement to ensure adequate resection margins and radicality.

Technically, most patients underwent surgery using five trocars, which facilitated manipulation in the deep pelvis. Selective lateral pelvic lymph node dissection was performed in 15.48% of patients according to indication, including bilateral, left-sided, or right-sided lateral pelvic lymph node dissection depending on suspicious lesions on imaging. Protective loop ileostomy was performed in 21.95% of cases, mainly in patients with low anastomoses or a high risk of anastomotic leakage.

The intraoperative complication rate was 5.36%, with presacral venous injury being the most common. Other complications included bleeding from the dissection plane, injury to the left ureter, obturator nerve, spleen, and left iliac vein. Most complications were promptly managed. The conversion rate to open surgery was 2.38%, mainly due to vascular complications, extensive tumor invasion, or technical difficulty in a narrow pelvis. This rate indicates that laparoscopic surgery after long-course LC-CRT remains feasible and safe when performed by an experienced surgical team.

The mean operative time was 133.4 ± 33.7 minutes, and the mean blood loss was 71.1 ± 107.8 mL. Operative time in the lower rectal tumor group

was longer than that in the middle rectal tumor group, reflecting the greater technical difficulty of low pelvic dissection, particularly after LC-CRT.

4.2.2. Early Outcomes

The mean postoperative pain duration was 2.71 ± 1.0 days. Postoperative pain usually decreased markedly after the first few days, consistent with the minimally invasive advantage of laparoscopic surgery. Cases with prolonged pain were often associated with difficult surgery, low anastomosis, splenic flexure mobilization, or postoperative complications.

The overall early complication rate was 18.90%. The most common complications were urinary retention in 6.71%, anastomotic leakage in 4.96%, and surgical site infection in 3.66%. Other complications, such as wound bleeding, early bowel obstruction, and ureteral fistula, occurred at low rates. According to the Clavien–Dindo classification, most complications were grade I–II; 3.66% required reoperation, and no grade IV–V complication or postoperative mortality was recorded.

Anastomotic leakage was observed in 6 cases, accounting for 4.96%, all occurring early from postoperative day 2 to day 4. Most cases occurred in male patients with low rectal tumors who underwent intersphincteric resection and coloanal anastomosis. These leakage cases were detected early and managed by transanal anastomotic repair, laparoscopic abdominal lavage, and protective loop ileostomy; thus, the anastomosis was preserved. This result highlights the important role of early detection and active management in preserving low anastomoses.

The mean postoperative hospital stay was 10.9 ± 5.5 days. Hospital stay was influenced by postoperative complications, pain severity, recovery of gastrointestinal transit, and the patient's general condition.

4.2.3. Long-Term Outcomes

The mean follow-up duration was 48.8 ± 15.3 months, ranging from 5 to 80 months. This was a sufficiently long period to evaluate late complications, recurrence, metastasis, and survival after multimodal treatment.

Regarding anal sphincter function, the Wexner score showed that severe and very severe defecatory dysfunction was common during the first postoperative month, particularly in patients with very low anastomoses. However, function gradually improved over time; after one year, most

patients had only mild dysfunction, and further improvement continued to be observed at subsequent follow-up time points. This result is consistent with the pattern of functional recovery after low rectal resection, in which pelvic floor rehabilitation, dietary adjustment, antidiarrheal medication, and periodic functional follow-up play important roles.

Common late complications included parastomal hernia in 9.30%, anastomotic stricture in 5.79%, late anastomotic leakage in 3.31%, and adhesive partial bowel obstruction in 1.83%. Some rare complications included bladder atony, left ureteral stricture causing loss of left renal function, rectourethral fistula, and necrotizing inflammation of the anastomosis. Late anastomotic leakage occurred mainly in patients with low RC who underwent intersphincteric resection and coloanal anastomosis. Some cases responded to abscess drainage and antibiotics, whereas severe cases required dismantling of the anastomosis and creation of a permanent stoma. This suggests that preoperative radiotherapy may exert long-term effects on microcirculation and tissue healing at the anastomotic site.

The rate of local recurrence and/or distant metastasis in this study was 17.6%. The 1-year, 3-year, and 5-year disease-free survival rates were 95.7%, 85.6%, and 80.7%, respectively. Most recurrences or metastases occurred within the first 2–3 years after surgery, consistent with the natural course of RC progression after multimodal treatment.

Prognostic analysis showed that pathological response according to the Mandard classification was the strongest factor associated with the risk of recurrence/metastasis. Compared with the TRG 1 group, the TRG 4 and TRG 5 groups had a markedly increased risk of recurrence/metastasis. This confirms that TRG not only reflects the degree of response after LC-CRT, but also serves as an important indicator of tumor biology and residual disease burden. In addition, the quality of the total mesorectal excision specimen and post-LC-CRT CEA > 5 ng/mL were also independent prognostic factors for recurrence/metastasis. These results emphasize the combined role of histopathological response, surgical quality, and biological markers in predicting long-term outcomes.

The overall survival rate after surgery was 99.4% at 1 year, 91.1% at 3 years, and 82.7% at 5 years. This is a favorable result in the context that most

patients had locally advanced disease before treatment. The OS rate gradually decreased with poorer MRI response, suboptimal quality of the total mesorectal excision specimen, and higher postoperative disease stage. Multivariate analysis showed that an interval of less than 6 weeks from completion of LC-CRT to surgery, post-LC-CRT CEA > 5 ng/mL, and poor histopathological response were adverse prognostic factors for overall survival.

Overall, the study results indicate that LC-CRT combined with laparoscopic radical surgery for locally advanced middle and low RC is a safe, feasible, and effective treatment strategy. This regimen improves symptoms, reduces tumor size, downstages the disease, achieves a considerable complete response rate, and maintains a high rate of successful laparoscopic surgery, acceptable complications, and favorable survival outcomes. Factors such as TRG, post-LC-CRT CEA level, quality of the total mesorectal excision specimen, and timing of surgery after LC-CRT should be emphasized in prognostic assessment and in the individualization of postoperative treatment strategies.

CONCLUSIONS

Based on the study of 168 patients with stage II–III middle and low RC who underwent LC-CRT combined with radical laparoscopic surgery, the following conclusions were drawn:

1. Pathological Characteristics and Effectiveness of LC-CRT

The mean age of the patients was 62.0 years, with a male predominance of 69.64%. The most common pathological symptoms were bloody stool (92.86%) and weight loss (55.36%); the mean time from disease detection was 5.14 months. Pre-treatment MRI showed that cT3 invasion was predominant, accounting for 71.4%, and peritumoral lymph nodes were detected in 95.24% of patients. Elevated pre-treatment CEA levels (> 5 ng/mL) were observed in 40.48% of cases. Before LC-CRT, 95.24% of patients were diagnosed as stage III.

LC-CRT for middle and low RC was a safe treatment, with a protocol completion rate of 98.81%. Toxicities and adverse effects were low, mainly grade 1–3, and no grade 4–5 toxicity was recorded.

The effectiveness of long-course LC-CRT was demonstrated by complete resolution of symptoms in 41.1% of patients and near-complete improvement in 55.9%. Post-LC-CRT MRI showed that the rates of T3 and T4 invasion decreased to 60.7% and 4.8%, respectively; no tumor was visible in 7.1% of patients. The mean tumor size decreased from 5.6 cm before LC-CRT to 4.2 cm after LC-CRT ($p < 0.001$). The mean number of lymph nodes on MRI decreased from 5.1 before LC-CRT to 3.1 after LC-CRT ($p < 0.001$). Most patients achieved moderate response, classified as mrTRG 3 (46.43%), while 14.88% achieved complete response, classified as mrTRG 1. The sensitivity and specificity of mrTRG in predicting good histopathological response were 72.2% and 89.3%, respectively.

Histopathological results showed that 22.02% of patients achieved complete response, with no residual tumor cells in the specimen (TRG 1). The predominant invasion levels were ypT3 (34.52%) and ypT2 (33.33%). Postoperative disease downstaging was observed: 18.5% of patients were classified as stage 0, corresponding to complete response; 38.10% as stage I; 29.17% as stage II; and stage III decreased to 14.29%.

2. Outcomes of Laparoscopic Surgery for Middle and Low Rectal Adenocarcinoma Following LC-CRT

Intraoperative outcomes: Intraoperative assessment showed that tumor location was evenly distributed between the middle third (50.60%) and lower third (49.40%) of the rectum. Radiation-induced adhesions were observed in 42.86% of patients.

Laparoscopic surgery after long-course LC-CRT for middle and low RC was demonstrated to be safe and feasible, with a high rate of sphincter preservation. Only 23.21% of patients underwent Miles' operation. The intraoperative complication rate was low (5.36%), and 4 cases (2.38%) required conversion to open surgery. The mean operative time was 133.4 minutes, and the mean blood loss was 71.1 mL.

Early outcomes: Laparoscopic surgery contributed to reduced postoperative pain, with a mean duration of 2.71 days, and shortened postoperative hospital stay, with a mean duration of 10.9 days. Early complications were mainly grade I–II, accounting for 11.59%. Six cases

(3.66%) required reoperation, corresponding to grade IIIb. No severe complications, grade IV–V, were recorded. There was no intraoperative or postoperative mortality.

Long-term outcomes: With a mean long-term follow-up duration of 48.8 months, laparoscopic surgery for middle and low RC following preoperative LC-CRT demonstrated favorable oncological outcomes, with a local recurrence and/or distant metastasis rate of 17.6%. The 5-year overall survival (OS) and disease-free survival (DFS) rates were favorable, reaching 82.7% and 80.7%, respectively.

Univariate and multivariate analyses showed that the most important prognostic factors for recurrence/distant metastasis and overall survival were pathological response after LC-CRT, specimen quality, and post-LC-CRT CEA level. Poor pathological response according to the Mandard classification, particularly TRG 4 and TRG 5, increased the risk of recurrence/distant metastasis and death. Nearly complete specimen quality, poor differentiation, and post-LC-CRT CEA > 5 ng/mL were also independent prognostic factors associated with reduced overall survival.

RECOMMENDATIONS

LC-CRT in the treatment of middle and low RC improves the response rate, reduces tumor size and disease stage, and facilitates sphincter-preserving surgery. Laparoscopic surgery after long-course LC-CRT is a safe and effective method that can be implemented in surgical centers, provided that surgical techniques and multimodal treatment organization are standardized.

Future Research Directions

Further multicenter studies with larger sample sizes and longer follow-up periods are needed to confirm the prognostic value of mrTRG and post-treatment CEA.

Further studies should focus on sphincter-preserving strategies and postoperative functional improvement, particularly in patients undergoing intersphincteric resection.