Outcomes of neoadjuvant chemoradiotherapy for locally advanced rectal cancer under non-smoking conditions confirmed by measuring expiratory CO levels: An observational study

AKIRA INOUE[1], YOSHINORI KAGAWA[1,2], YUJIRO NISHIZAWA[1], TAKAMICHI KOMORI[3], MASAHIRO HASHIMOTO[1], YUKI OZATO[1], YOSHIHIRO MORIMOTO[1], SHIGETOSHI SHIMAMOTO[4], YASUHIRO MIYAZAKI[1], AKIRA TOMOKUNI[1], MASAAKI MOTOORI[1] and KAZUMASA FUJITANI[1]

[1]Department of Gastroenterological Surgery, Osaka General Medical Center, Osaka, Osaka 558-8558, Japan; [2]Department of Gastroenterological Surgery, Osaka International Cancer Institute, Osaka, Osaka 540-0008, Japan; [3]Department of Surgery, Hyogo Prefectural Nishinomiya Hospital, Nishinomiya, Hyogo 662-0918, Japan; [4]Department of Radiation Oncology, Osaka General Medical Center, Osaka, Osaka 558-8558, Japan

Received December 2, 2024; Accepted March 13, 2025

DOI: 10.3892/ol.2025.15012

Abstract. The outcomes of neoadjuvant chemoradiotherapy (CRT) under non-smoking conditions in patients with locally advanced rectal cancer (LARC) remain unclear. The aim of the present study was to evaluate the outcomes in patients with LARC who underwent neoadjuvant CRT under non-smoking conditions, followed by total mesorectal excision (TME). To this end, the medical records of 28 patients treated with CRT and surgery for LARC between January 2014 and December 2019 were retrospectively analyzed. Smoking cessation was monitored by measuring carbon monoxide (CO) levels using a Smokerlyzer. Survival outcomes and clinicopathological factors associated with pathological complete response (pCR) were investigated. The median age was 66 (45-89) years, and 20 (71.4%) patients were male. A total of 16 (57.1%) patients were diagnosed with clinical stage III LARC. Seven patients smoked at diagnosis, with an average expiratory CO level of 8 (8-30) ppm. These patients ceased smoking and maintained exhaled CO levels <3 ppm before treatment. All patients successfully underwent CRT and TME. No major postoperative complications occurred. pCR was achieved in 8/28 patients (28.6%) and the 5-year recurrence-free and overall survival rates were 78.0% [95% confidence interval (CI), 57.4-89.5] and 85.7% (95% CI, 66.3-94.4), respectively. The median follow-up period was 60.1 (range, 5.6-114.6) months. Survival did not significantly differ between smokers and non-smokers at diagnosis. Clinically negative N stage (hazard ratio: 18.9; 95% CI, 1.63-218; P=0.0187) was significantly associated with pCR. In conclusion, neoadjuvant CRT under non-smoking conditions, as confirmed by measuring expiratory CO levels, followed by TME yields favorable pCR rates and survival outcomes in patients with LARC.

Introduction

In 2020, 732,210 people had colorectal cancer in 185 countries, accounting for 339,022 deaths (1). Among colorectal cancer, locally advanced rectal cancer (LARC) poses significant treatment challenges due to its high risk of local recurrence and distant metastasis. In Western countries, neoadjuvant therapies, including chemoradiotherapy (CRT) and total neoadjuvant therapy (TNT), are the standard of care for LARC, aiming to facilitate tumor downstaging, improve local control, and reduce the risk of distant metastasis (2,3). Furthermore, CRT has also been widely utilized in the treatment of various locally advanced solid tumors, including gastrointestinal malignancies, head and neck, gynecological, lung, and genitourinary cancers, as well as for glioblastoma and sarcoma (4).

While CRT has significantly improved outcomes for LARC, treatment responses remain highly variable among patients. One of the factors that may influence the efficacy of CRT is cigarette smoking. Recent studies have shown that cigarette smoking during radiotherapy for glottic carcinomas and anal cancers is associated with poor therapeutic responses (5,6). Smoking during radiotherapy has

Correspondence to: Dr Yoshinori Kagawa, Department of Gastroenterological Surgery, Osaka General Medical Center, 3-1-56 Mandaihigashi, Sumiyoshi, Osaka, Osaka 558-8558, Japan
E-mail: yoshikagawa@gmail.com

Abbreviations: APR, abdominoperineal resection; CO, carbon monoxide; CEA, carcinoembryonic antigen; CRT, chemoradiotherapy; CT, computed tomography; CI, confidence interval; HR, hazard ratio; Hb, hemoglobin; ISR, intersphincteric resection; JSCCR, Japanese Society for Cancer of the Colon and Rectum classification; LLND, lateral lymph node dissection; LLNs, lateral lymph nodes; LARC, locally advanced rectal cancer; LAR, low anterior resection; MRI, magnetic resonance imaging; OS, overall survival; pCR, pathological complete response; TS-1, tegafur/gimeracil/oteracil; TME, total mesorectal excision; TNT, total neoadjuvant therapy

Key words: CRT, expiratory CO level, rectal cancer, smoking, Smokerlyzer

been linked to increased hypoxia, reduced radiosensitivity, and impaired treatment outcomes. However, the effect of smoking on CRT for rectal cancer remains unclear. In our institution, patients with LARC are strictly instructed to quit smoking before radiotherapy, and all patients are monitored for smoking cessation by measuring carbon monoxide (CO) levels in their exhaled breath using a Smokerlyzer prior to initiation of neoadjuvant CRT.

This study aimed to describe the outcomes of neoadjuvant CRT under strict non-smoking conditions, as confirmed by measuring CO levels, followed by total mesorectal excision (TME) in patients with LARC. By assessing treatment response rates and survival outcomes, this study seeks to provide valuable insights into the potential benefits of smoking cessation on neoadjuvant CRT efficacy for LARC. These findings could inform improvements in the treatment outcomes of patients with LARC undergoing neoadjuvant CRT.

Materials and methods

Ethics. This retrospective single-center observational study was approved by the institutional review board of Osaka General Medical Center (approval no. 2020-069; Osaka, Japan). Informed consent was obtained through an opt-out method on the website, by which any patient could refuse inclusion in the study.

Patients. We retrospectively included the data of patients with LARC (clinical stage II or III) who underwent neoadjuvant CRT and radical surgery between January 2014 and December 2019. The inclusion criteria were as follows: i) Histologically confirmed adenocarcinoma of the rectum, ii) tumors located below the peritoneal reflection, and iii) cT3/T4 and/or cN+ rectal cancer without distant metastasis. The clinical stage was determined based on imaging studies, including endoscopy, multi-slice computed tomography (CT), and magnetic resonance imaging (MRI). Lymph nodes with a short-axis diameter ≥10 mm on CT or MRI and/or a high-intensity spot on positron emission tomography CT images were considered suspicious for metastasis. Pre- and post-operative staging was performed according to the 9th edition of the Japanese Society for Cancer of the Colon and Rectum classification (JSCCR) (7). For lymph node assessment, lateral lymph nodes (LLNs) (i.e., obturator and sacral lymph nodes) were defined as regional lymph nodes. Metastasis in the inguinal lymph node was defined as distant unless the tumor extended to the anal canal.

Monitoring smoking cessation. Prior to the initiation of neoadjuvant CRT, smoking cessation guidance was provided to all patients who smoked at diagnosis. Complete smoking cessation was monitored using a Smokerlyzer (Bedfont Scientific Ltd., Kent, UK) (8), which quantified expiratory CO levels to detect whether patients had smoked within the past few days. Smoking cessation was defined as a maintained expiratory CO level of 0-3 ppm without an increase for 4 consecutive weeks. For patients with CO levels >3 ppm, CRT was postponed for 4 weeks. Four consecutive weeks after smoking cessation, CO levels were measured to ensure that smoking cessation was maintained.

Treatment strategy. CRT comprised a total radiation dose of 50.0 Gy (2.0 Gy/day, 5 days per week, for 5 weeks) and tegafur/gimeracil/oteracil (TS-1). The bilateral pelvic area, apart from the primary tumor and regional lymph nodes, was included in the radiation target area. Concomitant chemotherapy with TS-1 (80-120 mg/day) was orally administered on the day of radiotherapy for 5 weeks. Imaging examinations were performed 4-6 weeks after CRT, and the clinical stage was preoperatively determined.

Surgical resection was performed 8-12 weeks after completion of CRT. All patients underwent laparoscopic TME. Lateral lymph node dissection (LLND) was performed only in patients with suspected LLN metastases based on pretreatment images, regardless of the response of the lymph nodes to CRT. LLND was performed only on the side of the suspected LLNs; furthermore, the internal iliac, external iliac, and obturator regions were dissected following the standard LLND procedure. In the case of suspected bilateral metastases to LLNs, bilateral LLND was performed. Temporary ileostomy was performed at the discretion of each surgeon, as recommended by the multidisciplinary team.

Adjuvant chemotherapy was considered for patients with high-risk stages II and III. The decision was made by the attending physician.

Evaluation of clinical and pathological response to CRT. The clinical response to CRT was evaluated based on the Response Evaluation Criteria in Solid Tumors (RECIST 1.1).

The pathological primary tumor response to CRT was evaluated using a grading scale according to the JSCCR 9th edition. Grade 0 represents no response to treatment, grade 1a a tumor size reduction of 1/3, grade 1b a tumor size reduction of 1/3-2/3, grade 2 a tumor size reduction >2/3, and grade 3 complete tumor ablation. Grade 3 corresponds to pathological complete response (pCR) (7).

Follow-up. The patients were followed up at 3-month intervals during the first 3 years and at 6-month intervals thereafter for up to 5 years. Tumor markers carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 were assessed at each follow-up visit. CT scans were performed at 6-month intervals. Total colonoscopies were performed annually.

Statistical analysis. Continuous parameters are presented as mean, median, standard deviation, and interquartile range. Univariate and multivariate logistic regression analyses were used to evaluate factors associated with pCR. The Kaplan-Meier method was used to evaluate survival outcomes, and the log-rank test was used to assess the estimated survival rate. The hazard ratio (HR) was calculated using a Cox proportional hazards model, followed by the calculation of the 95% confidence interval (CI). Variables were included in the models based on the existing knowledge regarding risk factors for 5-year overall survival (OS). All statistical analyses were performed using R version 1.60 (SAS Institute Inc., Cary, NC, USA) and GraphPad Prism version 6.01 for Windows (GraphPad Software, San Diego, CA, USA). Statistical significance was assessed using 95% CI. Two-tailed $P<0.05$ was considered to indicate a statistically significant difference.

Table I. Patients' characteristics (n=28).

Variable	Value
Median age, years (range)	66 (45-89)
Sex, n (%)	
Male	20 (71.4)
Female	8 (28.6)
Median BMI, kg/m^2 (range)	22.4 (16.9-35.9)
History of smoking, n (%)	18 (64.3)
Median expiratory CO, ppm (range)	
Smoker at diagnosis (n=7)	8 (8-30)
After smoking cessation (n=7)	2 (1-3)
Median pretreatment CEA, ng/ml (range)	3.7 (1-47.1)
Median pretreatment Hb, g/dl (range)	13.0 (7.3-15.5)
Median tumor size, mm (range)	32.5 (0-70)
Median tumor location from AV, mm (range)	50 (0-100)
Circumferential involvement (<1/3), n (%)	3 (10.7)
Clinical N stage, n (%)	
Negative	12 (42.9)
Positive	16 (57.1)
Adverse events during CRT, n (%)	
Diarrhea (Grade 2)	1 (3.6)
Ileus (Grade ≥3)	1 (3.6)
Neutropenia (Grade ≥3)	1 (3.6)
Clinical response to CRT, n (%)	
cPR	24 (85.7)
cSD	3 (10.7)
cPD (occurrence of liver metastasis)	1 (3.6)
Adjuvant chemotherapy	
CAPOX	2 (7.1)
TS-1	12 (42.9)
UFT/LV	1 (3.6)

BMI, body mass index; CEA, carcinoembryonic antigen; Hb, hemoglobin; AV, anal verge; CRT, chemoradiotherapy; cPR, clinical partial response; cSD, clinically stable disease; cPD, clinically progressive disease; CAPOX; capecitabine and oxaliplatin; TS-1, tegafur/gimeracil/oteracil; UFT, tegafur-uracil; LV, folinic acid.

Table II. Surgical outcomes (n=28).

Variable	Value
Surgical procedure, n (%)	
APR	14 (50.0)
LAR	13 (46.4)
ISR	1 (3.6)
With LLND	4 (14.3)
Median operation time, min (range)	367.5 (203-552)
Median estimated blood loss, ml (range)	120 (0-1420)
Conversion to open surgery, n	0
Curative resection for primary tumor, n (%)	28 (100)
Postoperative complication, n (%)	
SSI	9 (32.1)
Anastomotic leakage	1 (3.6)
Paralytic ileus	3 (10.7)
Urinary dysfunction	2 (7.1)
Lymphatic leakage	2 (7.1)
Median postoperative hospital stay, days (range)	17 (9-77)
Postoperative mortality, n	0
Sites of recurrence, n (%)	
Local	1 (3.6)
Lung	3 (10.7)
Liver	3 (10.7)
Lateral lymph node	0

APR, abdominoperineal resection; LAR, low anterior resection; ISR, intersphincteric resection; LLND, lateral lymph node dissection; SSI, surgical site infection.

Results

Patient characteristics. Overall, 28 patients were included, with their characteristics summarized in Table I. The median age was 66 years, and 20 patients were male. Median tumor size and median tumor location from the anal verge were 32.5 and 50 mm, respectively. Sixteen patients were diagnosed with clinical stage III. Seven patients smoked at diagnosis. The average expiratory CO level was 8 (range, 8-30) ppm. After smoking cessation guidance, smoking cessation was confirmed based on an expiratory CO level <3 ppm within a month before CRT initiation.

CRT. All patients successfully underwent the scheduled CRT. During CRT, one patient experienced diarrhea (grade 2), with the TS-1 dose being reduced. A second and third patient experienced ileus (grade ≥3) and neutropenia (grade ≥3), respectively, with CRT treatment being temporarily discontinued in both patients. Clinical partial response was achieved in 24 patients, whereas one patient developed liver metastasis during CRT.

Surgical outcomes. Table II summarizes the surgical outcomes. Fourteen patients underwent abdominoperineal resection. LLND was performed in four patients with suspected LLN metastasis before CRT. There was no conversion to open surgery. Curative resection of the primary tumor was performed in all 28 patients, with a surgically sufficient circumferential resection margin. Among them, one patient who developed liver metastasis during neoadjuvant CRT underwent curative hepatectomy. There were no major complications defined as grade ≥3 according to the Clavien-Dindo classification.

Pathological findings. The pathological findings are summarized in Table III. Overall, pCR was achieved in 8/28 patients (28.6%; 95% CI, 15.1-47.2). LLN metastasis was

Table III. Pathological findings (n=28).

Variable	Value
Histological type, n (%)	
Well-/moderately differentiated	26 (92.9)
Mucinous/poorly differentiated/signet	2 (7.1)
ypT, n (%)	
ypT0	8 (28.6)
ypT1	0
ypT2	6 (21.4)
ypT3	14 (50.0)
ypT4	0
ypN, n (%)	
ypN0	20 (71.4)
ypN1	7 (25.0)
ypN2	0
ypN3	1 (3.6)
Pathological complete response, n (%)	8 (28.6)
Median number of lymph nodes resected (range)	12 (2-34)
Location of lymph node metastasis, n (%)	
Mesorectum	7 (25.0)
LLN	1 (3.6)
Positive lymphovascular invasion, n (%)	9 (32.1)
Positive circumferential resection margin, n	0

Pathological stage was classified according to the 9th edition of the Japanese Society for Cancer of the Colon and Rectum classification. LLN, lateral lymph node.

detected in one out of four patients who underwent LLND. None of the patients showed a positive circumferential resection margin.

Survival outcomes and clinicopathological factors associated with pCR. The median follow-up period was 60.1 months. The 5-year recurrence-free survival and OS rates were 78.0% (95% CI, 57.4-89.5) and 85.7% (95% CI, 66.3-94.4), respectively (Fig. 1). There was no significant difference in survival between patients with and without pCR (Fig. 2). One patient had local recurrence; three, including one with pCR, had lung recurrence; and three, including one with pCR, developed liver recurrence. No patient developed local recurrence at the LLN. Moreover, there was no significant difference in survival between smokers and non-smokers at diagnosis (Fig. S1).

Table IV shows the clinicopathological factors associated with pCR. Univariate analysis showed that pretreatment hemoglobin (Hb) (>13.0 g/dl) was associated with pCR (HR: 7.00; 95% CI: 1.09-45.2; P=0.0408). Multivariate logistic regression analysis showed that clinically negative N stage before treatment was significantly associated with pCR (HR: 18.9; 95% CI, 1.63-218.0; P=0.0187). However, being a non-smoker was not associated with pCR (HR: 0.417; 95% CI, 0.0687-2.53; P=0.341).

Discussion

To our knowledge, this is the first study to report the oncological outcomes in patients with LARC who underwent neoadjuvant CRT under strict non-smoking conditions. Neoadjuvant CRT under non-smoking conditions achieved favorable pCR rates and comparable survival outcomes. Additionally, a clinically negative N stage before treatment was significantly associated with pCR to neoadjuvant CRT.

Smoking creates hypoxic environment given an increase in the degree of carboxyhemoglobin saturation in the blood and tissue. Chronic hypoxia compromises the effects of radiotherapy, resulting in limited treatment efficacy (9). Browman *et al* (10) reported that patients with head and neck cancer who continued smoking during radiotherapy (n=53) had a lower complete response rate (45% vs. 74%, P=0.008) and poorer 2-year survival (39 vs. 66%, P=0.005) than those who did not smoke or quit before treatment (n=62). Their study suggested that smoking during therapy reduced the response to radiotherapy in patients with head and neck cancer. To improve the clinical outcomes of radiotherapy, complete smoking cessation, confirmed by monitoring expiratory CO levels using a Smokerlyzer, has contributed towards a lower relapse rate and better prognosis in various cancers (5,6). Thus, we used Smokerlyzer to monitor smoking cessation. Smokers at diagnosis who quit smoking before radiotherapy showed expiratory CO levels within the reference range and had outcomes similar to those of non-smokers, highlighting the potential benefit of smoking cessation before radiotherapy.

Neoadjuvant CRT reduces the local recurrence rate in patients undergoing LARC, with previous studies reporting pCR rates of 5.3% (11), 14.6% (12), 15.6% (13), and 19.2% (14). In this study, clinical partial response was achieved in 24/28 patients (85.7%); pCR was achieved in 8/28 patients (28.6%), which was higher than that achieved in these previous studies. A good pathological response to neoadjuvant CRT is associated with prolonged OS (14,15). Furthermore, achieving pCR after CRT is a valid surrogate of a favorable outcome regarding local control, distant recurrence, disease-free survival, and OS (14). Therefore, we investigated the predictive factors associated with pCR to neoadjuvant CRT. Univariate analysis showed that high pretreatment Hb (>13.0 g/dl) was associated with an increased pCR rate. Additionally, multivariate analysis revealed that clinically negative N stage before treatment was significantly associated with an increased pCR rate. These results are consistent with previous reports showing that pCR is associated with smaller tumor size, clinically negative N stage, higher radiation dose, and lower pretreatment CEA level (13,16-18). However, predictive factors of the pathological response to neoadjuvant CRT in patients with LARC are lacking.

Another possible reason for the high pCR rate in this study is the maintenance of the Hb level. A previous retrospective study suggested that Hb levels were significantly associated with disease-free survival in patients with rectal cancer who received neoadjuvant CRT (19). Moreover, clinical downstaging was achieved in 55 and 35% of patients with Hb levels >12 g/dl and <12 g/dl, respectively. Accordingly, we attempted to maintain the pretreatment Hb level by transfusion or

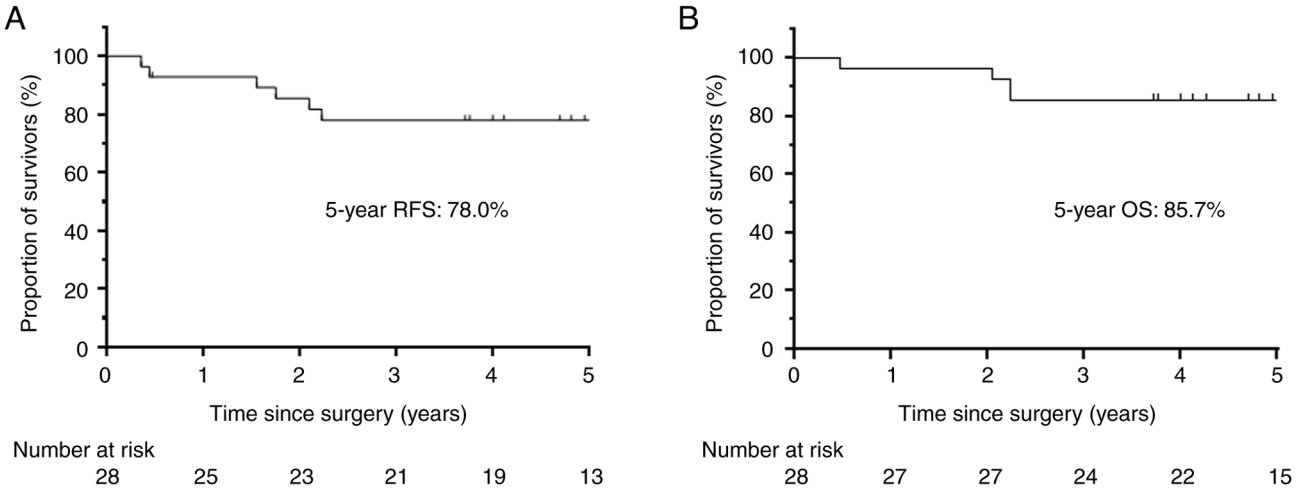

Figure 1. Kaplan-Meier survival curves following total mesorectal excision. (A) RFS. (B) OS. OS, overall survival; RFS, recurrence-free survival.

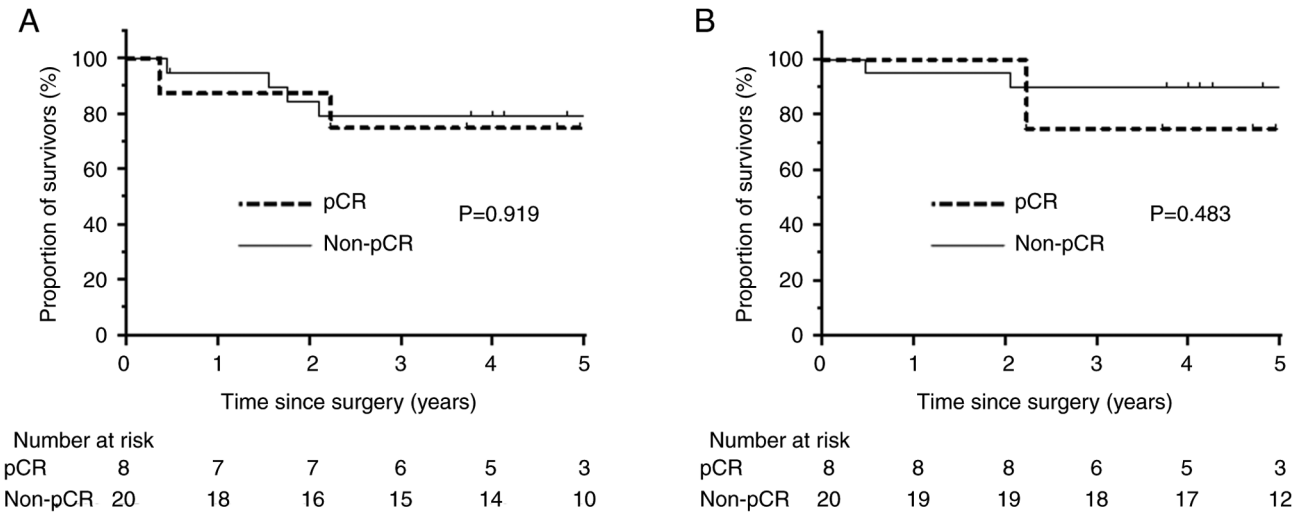

Figure 2. Kaplan-Meier survival curves following total mesorectal excision in patients stratified by pCR. (A) Recurrence-free survival stratified by pCR status. (B) Overall survival stratified by pCR status. pCR, pathological complete response.

prescribing oral iron tablets. We speculate that maintaining both high Hb levels and low CO levels under non-smoking conditions significantly contributed to high pCR rates and favorable outcomes in this study.

In our study, only one patient had local recurrence, and no recurrence was observed in the LLN region. However, distant metastases developed in 6/28 (21.4%) patients, including one patient who developed liver metastasis during neoadjuvant CRT. These results indicated that despite achieving good local control, including in the LLN region, distant metastases were not adequately controlled. An alternative treatment strategy known as TNT shows promise for improving both pCR rates and disease-free survival in patients with LARC (20). Recent evidence suggests that TNT may also increase the likelihood of achieving a complete clinical response, allowing for a non-operative management strategy in selected cases (21,22). Although TNT is promising for improving oncological outcomes, further studies are required to determine its long-term effects on local control and survival.

In our cohort, 14 patients (50%) underwent abdominoperineal resection (APR), while only 1 (3.6%) underwent intersphincteric resection (ISR). The high frequency of APR was primarily due to tumor invasion into the sphincter complex, making sphincter preservation unfeasible in many cases. Additionally, some patients who were eligible for ISR or low anterior resection (LAR) opted for APR to avoid potential postoperative functional impairment. LAR and ISR are associated with LAR syndrome, which includes symptoms such as frequent defecation, urgency, and fecal incontinence. Furthermore, neoadjuvant CRT can exacerbate these functional impairments by inducing radiation-associated fibrosis and neuropathy, which negatively impact sphincter control and anorectal compliance. Given these concerns, APR was chosen as a definitive approach to ensure a better long-term quality of life in selected patients.

This study has some limitations. First, this was a single-arm single-center retrospective observational study. Second, this study had a small sample size. Therefore, a

Table IV. Univariate and multivariate logistic regression analyses of factors associated with pCR.

	Univariate		Multivariate	
Factor	HR (95% CI)	P-value	HR (95% CI)	P-value
Age				
≤75 years	Reference	0.643		
>75 years	0.571 (0.054-6.08)			
Sex				
Female	Reference	0.792		
Male	1.290 (0.199-8.29)			
BMI				
≤25 kg/m^2	Reference	0.3410		
>25 kg/m^2	2.400 (0.396-14.600)			
Smoking at diagnosis				
Smoker	Reference	0.341		
Non-smoker	0.417 (0.0687-2.53)			
Pretreatment CEA levels				
≤5 ng/ml	Reference	0.9010		
>5 ng/ml	1.110 (0.203-6.11)			
Pretreatment Hb				
≤13.0 g/dl	Reference	0.0408	Reference	0.110
>13.0 g/dl	7.00 (1.090-45.20)		5.99 (0.665-54.0)	
Tumor size				
≤50 mm	Reference	0.475		
>50 mm	0.429 (0.0418-4.39)			
Tumor location from AV				
>40 mm	Reference	0.63		
≤40 mm	1.50 (0.288-7.81)			
Circumferential involvement				
≤1/3	Reference	0.847		
>1/3	0.778 (0.0605-10.00)			
Clinical N stage				
Positive	Reference	0.0103	Reference	0.0187
Negative	21.0 (2.05-215)		18.9 (1.63-218.0)	
Histological type				
Well/moderate	Reference	0.500		
Mucinous/poor/signet	2.71 (0.149-49.50)			
CRT				
Completion of CRT	Reference	0.847		
Incompletion of CRT	1.29 (0.100-16.5)			

pCR, pathologic complete response; BMI, body mass index; CI, confidence interval; CEA, carcinoembryonic antigen; Hb, hemoglobin; AV, anal verge; CRT, chemoradiotherapy.

large multicenter prospective study is required to evaluate the outcomes in patients with LARC who are treated with neoadjuvant CRT under non-smoking conditions. Third, we did not compare between current smokers and non-smokers during radiotherapy. This is because all the included patients successfully quit smoking prior to the initiation of neoadjuvant CRT. Based on the established benefit of smoking cessation for radiotherapy in other tumors, our institutional policy is to guide all patients quitting smoking before radiotherapy and monitor smoking cessation before starting neoadjuvant CRT. Another limitation is that all patients underwent laparoscopic TME, whereas robotic-assisted surgery was not performed in any case. In Japan, robotic-assisted surgery for rectal cancer has been covered by the national insurance system since 2018, whereas robotic-assisted surgery for colon cancer

was included in 2022. However, during our study period (2014-2019), robotic-assisted surgery was not widely available owing to high costs and limited institutional experience. Recent studies suggest that robotic-assisted surgery offers superior outcomes, particularly in male patients with mid- to low-rectal cancer, owing to its enhanced precision and improved ergonomics in narrow pelvic spaces (23-25).

In conclusion, neoadjuvant CRT under strict non-smoking conditions, as confirmed by measuring expiratory CO levels, yielded favorable pCR rates and comparable survival outcomes in patients with LARC.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

AI, YK, YN, TK, MH, YO, YMo, SS, YMi, AT, MM, and KF contributed to the conception and design. Material preparation, data collection and analysis were performed by AI, YK and YN. AI, YK and YN confirm the authenticity of all the raw data. The first draft of the manuscript was written by AI and YK, and all authors commented on previous versions of the manuscript. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

This retrospective single-center observational study was approved by the Institutional Review Board of Osaka General Medical Center (approval no. 2020-069). Informed consent was obtained through an opt-out method on the website, by which any patient could refuse inclusion in the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F: Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71: 209-249, 2021.
2. Sauer R, Becker H, Hohenberger W, Rödel C, Wittekind C, Fietkau R, Martus P, Tschmelitsch J, Hager E, Hess CF, *et al*: Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 351: 1731-1740, 2004.
3. Benson AB, Venook AP, Al-Hawary MM, Arain MA, Chen YJ, Ciombor KK, Cohen S, Cooper HS, Deming D, Garrido-Laguna I, *et al*: NCCN guidelines insights: Rectal cancer, version 6.2020. J Natl Compr Canc Netw 18: 806-815, 2020.
4. Rallis KS, Lai Yau TH and Sideris M: Chemoradiotherapy in cancer treatment: Rationale and clinical applications. Anticancer Res 41: 1-7, 2021.
5. Tatekawa S, Shimamoto S, Miyata Y, Yoshino Y, Hirata T, Tamari K, Seo Y, Isohashi F, Yamamoto Y, Uno A, *et al*: Monitoring expiratory carbon monoxide to study the effect of complete smoking cessation on definitive radiation therapy for early stage glottic carcinoma. Acta Oncol 60: 582-588, 2021.
6. Lerman J, Hennequin C, Etienney I, Abramowitz L, Goujon G, Gornet JM, Guillerm S, Aparicio T, Valverde A, Cattan P and Quéro L: Impact of tobacco smoking on the patient's outcome after (chemo)radiotherapy for anal cancer. Eur J Cancer 141: 143-151, 2020.
7. Japanese Society for Cancer of the Colon and Rectum: Japanese classification of colorectal, appendiceal, and anal carcinoma: The 3d English edition [secondary publication]. J Anus Rectum Colon 3: 175-195, 2019.
8. Deveci SE, Deveci F, Açik Y and Ozan AT: The measurement of exhaled carbon monoxide in healthy smokers and non-smokers. Respir Med 98: 551-556, 2004.
9. Nordsmark M and Overgaard J: Tumor hypoxia is independent of hemoglobin and prognostic for loco-regional tumor control after primary radiotherapy in advanced head and neck cancer. Acta Oncol 43: 396-403, 2004.
10. Browman GP, Wong G, Hodson I, Sathya J, Russell R, McAlpine L, Skingley P and Levine MN: Influence of cigarette smoking on the efficacy of radiation therapy in head and neck cancer. N Engl J Med 328: 159-163, 1993.
11. Akagi T, Inomata M, Fujishima H, Fukuda M, Konishi T, Tsukamoto S, Teraishi F, Ozawa H, Tanaka K, Hida K, *et al*: Preoperative chemoradiotherapy versus surgery alone for advanced low rectal cancer: A large multicenter cohort study in Japan. Surg Today 50: 1507-1514, 2020.
12. Huh JW, Kim HR and Kim YJ: Clinical prediction of pathological complete response after preoperative chemoradiotherapy for rectal cancer. Dis Colon Rectum 56: 698-703, 2013.
13. Maas M, Nelemans PJ, Valentini V, Das P, Rödel C, Kuo LJ, Calvo FA, García-Aguilar J, Glynne-Jones R, Haustermans K, *et al*: Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: A pooled analysis of individual patient data. Lancet Oncol 11: 835-844, 2010.
14. Sadahiro S, Suzuki T, Tanaka A, Okada K, Saito G, Kamijo A, Akiba T and Kawada S: Phase II study of preoperative concurrent chemoradiotherapy with S-1 plus bevacizumab for locally advanced resectable rectal adenocarcinoma. Oncology 88: 49-56, 2015.
15. Tomono A, Yamashita K, Kanemitsu K, Sumi Y, Yamamoto M, Kanaji S, Imanishi T, Nakamura T, Suzuki S, Tanaka K and Kakeji Y: Prognostic significance of pathological response to preoperative chemoradiotherapy in patients with locally advanced rectal cancer. Int J Clin Oncol 21: 344-349, 2016.
16. Garland ML, Vather R, Bunkley N, Pearse M and Bissett IP: Clinical tumour size and nodal status predict pathologic complete response following neoadjuvant chemoradiotherapy for rectal cancer. Int J Colorectal Dis 29: 301-307, 2014.
17. Huang CM, Huang CW, Ma CJ, Yeh YS, Su WC, Chang TK, Tsai HL, Juo SH, Huang MY and Wang JY: Predictive value of FOLFOX-based regimen, long interval, hemoglobin levels and clinical negative nodal status, and postchemoradiotherapy CEA levels for pathological complete response in patients with locally advanced rectal cancer after neoadjuvant chemoradiotherapy. J Oncol 2020: 9437684, 2020.
18. Al-Sukhni E, Attwood K, Mattson DM, Gabriel E and Nurkin SJ: Predictors of pathologic complete response following neoadjuvant chemoradiotherapy for rectal cancer. Ann Surg Oncol 23: 1177-1186, 2016.
19. Berardi R, Braconi C, Mantello G, Scartozzi M, Del Prete S, Luppi G, Martinelli R, Fumagalli M, Valeri G, Bearzi I, *et al*: Anemia may influence the outcome of patients undergoing neo-adjuvant treatment of rectal cancer. Ann Oncol 17: 1661-1664, 2006.

20. Conroy T, Bosset JF, Etienne PL, Rio E, François É, Mesgouez-Nebout N, Vendrely V, Artignan X, Bouché O, Gargot D, *et al*: Neoadjuvant chemotherapy with FOLFIRINOX and preoperative chemoradiotherapy for patients with locally advanced rectal cancer (UNICANCER-PRODIGE 23): A multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 22: 702-715, 2021.
21. Asoglu O, Bulut A, Aliyev V, Piozzi GN, Guven K, Bakır B and Goksel S: Chemoradiation and consolidation chemotherapy for rectal cancer provides a high rate of organ preservation with a very good long-term oncological outcome: A single-center cohort series. World J Surg Oncol 20: 358, 2022.
22. Asoglu O, Goksoy B, Aliyev V, Mustafayev TZ, Atalar B, Bakir B, Guven K, Demir G and Goksel S: Watch and wait strategy for rectal cancer: How long should we wait for a clinical complete response? Surg Technol Int 40: 130-139, 2022.
23. Aliyev V, Goksel S, Bakir B, Guven K and Asoglu O: Sphincter-saving robotic total mesorectal excision provides better mesorectal specimen and good oncological local control compared with laparoscopic total mesorectal excision in male patients with mid-low rectal cancer. Surg Technol Int 38: 160-166, 2021.
24. Aliyev V, Piozzi GN, Shadmanov N, Guven K, Bakır B, Goksel S and Asoglu O: Robotic and laparoscopic sphincter-saving resections have similar peri-operative, oncological and functional outcomes in female patients with rectal cancer. Updates Surg 75: 2201-2209, 2023.
25. Aliyev V, Piozzi GN, Huseynov E, Mustafayev TZ, Kayku V, Goksel S and Asoglu O: Robotic male and laparoscopic female sphincter-preserving total mesorectal excision of mid-low rectal cancer share similar specimen quality, complication rates and long-term oncological outcomes. J Robot Surg 17: 1637-1644, 2023.