Original Article

The Long-term Clinical Outcomes of Neoadjuvant Concurrent Radiochemotherapy for Treatment of Locally Advanced Colon Cancer

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Key Words
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Purpose. Locally advanced colon cancer remains a challenge of radical resection, because it is associated with poor oncologic outcomes. Neoadjuvant concurrent chemoradiotherapy can improve the curative resection rate and patient's survival. This study evaluated the related treatment efficiency, toxicity, pathologic features and long-term survival period.
Methods. We reviewed 36 patients diagnosed with locally advanced colon cancer and who received treatment between January 2012 and January 2017. We retrospectively analyzed the treatment details and outcomes from medical records. All patients received neoadjuvant concurrent chemoradiotherapy. The neoadjuvant chemotherapy regiment included oxaliplatin, folinic acid and 5-fluorouracil.
Results. The proportion of T and N downstaging was 63.9% and 86.1% respectively. Anemia (18.89%) was the most common Grade 3 adverse events, followed by leukopenia (16.67%). Most of the adverse events were manageable through symptomatic treatment. Of 36 patients, 34 underwent surgery after concurrent chemoradiotherapy, and the remaining 2 patients were still unresectable. However, 1 patient had 3 synchronous locally advanced colon cancer and received tumor resection successfully. A logistic regression analysis demonstrated that local recurrence and distant metastasis were independent predictor of survival (all $p < 0.05$). Estimated 5-year overall survival rate was 66% and disease-free survival rate was 43%. Eight patients (22.2%) presented a pathologic complete response. Patients with pathologic complete response or no lymph node invasion on specimen had longer overall survival and disease-free survival periods, but without significance (both $p > 0.05$). For patients with pathologic complete response, the local recurrence rate was 0, but 3 patients (37.5%) developed distant metastasis subsequently.
Conclusions. Neoadjuvant chemoradiotherapy was a feasible and safe treatment strategy for locally advanced colon cancer, and patients with pathologic complete response and no lymph node invasion on specimen had longer survival periods. No local recurrence was noted in patients with pathologic complete response, but with distant metastasis risk.
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Colorectal cancer (CRC), aglobally prevalent malignant disease with rapid growth is the second and third commonly diagnosed cancer in women and men respectively.[1] In Taiwan, CRC is currently the most common cancer and the third leading cause of cancer-related deaths.[2] Standard curative therapy for CRC is complete resection with a negative margin. However, this target is difficult to achieve when treating locally advanced colon cancer (LACC). LACC typically presents infiltration and invasion into the surrounding organs or structures, and extensive lymph node metastasis near the root of the feeding artery. These features pose a challenge for curative resection. Currently, LACC treatment outcome remains unsatisfactory. The 5-year survival rates of patients with stage IIC, IIIB, and IIIC LACC were 37.3%, 46.3% and 28%, respectively.[3] Consequently, treatment strategies other than radical resection have been widely discussed. However, neoadjuvant concurrent chemoradiotherapy (CCRT) is now the optional treatment for locally advanced rectal cancer, and therapeutic effects have been proved in randomized control trials.[4,5]

The Chinese Neoadjuvant FOLFOX6 Chemotherapy With or Without Radiation in Rectal Cancer (FOWARC) randomized phase III trial applied neoadjuvant 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX)-based CCRT to patients with advanced rectal cancer. The result was promising with a high pathologic complete response (pCR) rate of 14.0%-27.5%.[6] However, this study did not mention the effects of neoadjuvant radiotherapy. Post-operative radiotherapy was thought to improve disease control in patients with LACC.[7,8] The Intergroup Protocol 0130 trial demonstrated no difference in the overall survival (OS) and disease-free survival (DFS) between LACC patients receiving postoperative chemotherapy alone and those receiving postoperative CCRT.[9] Tangible evidence for the efficiency of radiotherapy before surgery for LACC is lacking. We previously reported that neoadjuvant FOLFOX-based CCRT is an effective treatment approach for LACC, with the pCR rate of surgery after CCRT was 31.6%.[10] Here, we analyzed characteristics, toxicity, pathologic features and survival periods of oncologic outcomes of neoadjuvant FOLFOX-based CCRT in patients with LACC.

Materials

Between January 2012 and January 2017, we enrolled 36 patients diagnosed as having LACC. Multidisciplinary cancer conferences have recommended that patients with potentially suitable for complete resection or neoadjuvant CCRT. The definition of LACC is a T3 tumor with extramural extension of > 5 mm or a tumor with clinical stage of T4 or extensive lymph node metastasis near the root of the feeding artery. Other inclusion criteria were colon cancer located ≥ 15 cm from the anal verge, an Eastern Cooperative Oncology Group score of 0-2, and no evidence of distant metastasis at diagnosis. The exclusion criteria were a history of synchronous malignancies other than non-melanoma skin cancer and the presence of serious medical comorbidities that may influence treatment compliance. We reviewed the medical records and analyzed patients' characteristics, treatment efficacy and toxicity, details of surgery, pathological features, and long-term survival. The present study was approved by the Institutional Ethics Committee of our hospital. Pretreatment evaluation entailed a complete medical history review and physical examination, colonoscopy, tumor biopsy, chest radiography, abdominal and pelvic computed tomography (CT) with or without magnetic resonance imaging, serum carcinoembryonic antigen (CEA) level assessment, and routine laboratory tests.

Preoperative treatment

The chemotherapy regiment was based on FOLFOX. Each FOLFOX cycle comprises 85 mg/m^2 oxaliplatin and 400 mg/m^2 folinic acid infusion on day 1, followed by a 46-h infusion of 2800 mg/m^2 5-fluorouracil (5-FU). This regiment was applied to all patients every 2 weeks. Among all patients, 2 patients did not receive radiotherapy. Other patients received CCRT: after completion of radiotherapy, the patients received chemotherapy biweekly until surgery.

All the patients underwent a planning CT in the supine position and were immobilized with custom thermoplastic immobilization devices before radiotherapy was initiated. Target volumes were delineated

according to the International Commission on Radiation Units and Measurements reports 62.[11] The gross tumor volume (GTV) was defined as the macroscopic tumor and enlarged lymph nodes visible on diagnostic CT images. The clinical target volume (CTV) was the GTV plus a 15-20-mm margin, and the planning target volume was the CTV plus a 10-15-mm margin. Organs at risk (OARs), such as the kidneys, small bowel, liver, and spinal cord, were contoured. A radiation dose of 45-50.4 Gy was administered in 25-28 fractions. The dose constraints for OARs were as follows: the volume of liver receiving ≥ 30 Gy of radiation was maintained at < 30%, the mean dose for the kidney was restricted to < 15 Gy, and the volume of the kidney receiving ≥ 20 Gy was maintained at < 30%. The volume of the small bowel receiving > 50 Gy was limited to < 1 mL, and the maximal dose to the spinal cord was restricted to < 45 Gy.

Surgery and pathology review

Patients underwent elective surgery at > 6 weeks after the completion of radiotherapy. Pathologic features included tumor (T) and nodal (N) stages (ypT and ypN, respectively), histological grade, lymphovascular invasion, perineural invasion, and tumor regression grade (TRG), and the status of the circumferential, proximal, and distal resection margins was documented. The tumor response after CCRT was assessed according to the American Joint Committee on Cancer system as follows:[12] Grade 0, no residual cancer cells; Grade 1, a single cell or small group of cancer cells (major regression); Grade 2, residual cancer with desmoplastic response (moderate regression); and Grade 3, minimal evidence of tumor response. A circumferential resection margin (CRM) of < 1 mm was defined as an involved CRM.[13] pCR was defined as the absence of viable cancer cells in the pathological specimens, including primary tumor and lymph nodes (ypT0N0), after neoadjuvant CCRT.

Toxicity evaluation and follow-up

During CCRT and in postoperative follow-up, acute adverse events (AEs) at each visit were graded according to the Common Terminology Criteria for Adverse Events (version 4.0). Late radiation toxicity was scored using the Radiation Therapy Oncology Group Late Radiation Morbidity Scoring System. After surgery, patients were followed monthly for 6 months and subsequently once in every 2-3 months thus far.

Endpoints and statistics

Downstaging was determined according to the response between the clinical T or N stage before neoadjuvant CCRT and the postoperative pathological T or N stage. Descriptive statistics are presented as proportions and means. The chi-square and Fisher exact tests were used to compare categorical data, whereas normally distributed continuous variables were analyzed using the Student t test. DFS was measured from the date of CCRT initiation until the date of any type of recurrence or final follow-up. OS was measured from the date of CCRT initiation until date of death due to any cause or final follow-up. Survival rates were estimated using the Kaplan-Meier method. Data analyses were performed using SPSS (version 20; International Business Machines Corporation, Armonk, USA).

Result

Patient characteristics

This study included 36 patients and 36 colon neoplasms. One 45-year-old man sustained 3 synchronous advanced colon cancer tumors on the cecum and ascending and sigmoid colon. The median (range) age was 64 (45-86) years. Most tumors were located on the sigmoid colon (50.0%) followed by the ascending colon (30.8%). One fourth of the tumors invaded initially to other organs, such as the bladder or uterus. All patients exhibited positive lymph node invasion, except 1 that was nodal negative (T4aN0) on imaging results. The median CEA level before the treatment was 4.4 ng/mL, but its range was from 0.6 to 649 mg/mL. Approximately half of the patients' CEA levels were ≥ 5 ng/mL. After the treatment, CEA levels decreased or remained stable in most patients: only 1 pa-

tient showed mild elevation from 2.89 to 5.79 ng/mL. Twenty-three (63.9%) patients required colostomy or ileostomy as bridge treatment for bowel obstruction. The patient and treatment characteristics are listed in Table 1.

Radiotherapy

The radiotherapy dose was between 45 and 50.4 Gy in 25-28 fractions. Four patients received 3-dimensional conformal radiotherapy using either 3 or 4 fields. Four patients received volumetric-modulated arc therapy. Rapid arc (RA) and helical tomotherapy were administered to 15 and 11 patients, respectively. Among all patients, 2 patients did not receive radiotherapy. One patient received a split dose with 3400 cGy/17 fx and 5000 cGy/25 fx. They were excluded while calculating radiotherapy-related data related to radiotherapy. The median neoadjuvant radiotherapy duration was 35 days. The median (range) cycle of chemotherapy was 7 (3-13 cycles) for the treatment course. The median (range) number of concurrent chemotherapy cycles during the radiotherapy was 3 (2-4). After the patient completed the radiotherapy course, we maintained chemotherapy biweekly until 2 weeks before surgery. The differences in cycle numbers were related to tumor resectability, AEs or disease progression. The average time interval between radiotherapy completion and the surgery was 78 days. The summary of radiotherapy is listed in Table 2.

Table 1. Summary and characters of the patients (patient = 36, tumor = 36)[a]

Characteristic	
Age (years, median) (range)	64.00 (45-86)
Gender	
Male	20 (55.5%)
Female	16 (44.4%)
BMI kg/m^2 (mean) (range)[b]	22.27 (15.61-34.02)
Location	
Cecum	4 (11.1%)
Ascending colon	11 (30.8%)
Transverse colon	3 (8.3%)
Sigmoid colon	18 (50%)
Clinical tumor depth	
T3	14 (36.8%)
T4a	15 (39.5%)
T4b	9 (23.7%)
Clinical lymph node metastasis	
N0	1 (2.6%)
N1	18 (47.4%)
N2	19 (50%)
AICC staging[c]	
IIC	1 (2.6%)
IIIB	19 (50%)
IIIC	18 (47.4%)
Pretreatment CEA (ng/mL) (median)[d]	4.4 (0.6-649)
CEA ≤ 5	
Yes	19 (52.8)
No	17 (47.2)
CEA decrease	
Decrease	17 (47.2)
Stable	18 (50.0)
Increase	1 (2.8)
Ileosotmy/colostomy prior to therapy	
Yes	23 (63.9%)
No	13 (36.1%)

[a] In 36 patients, 2 failed to receive surgical resection. 1 patient had 3 synchronous advanced colon cancer; [b] BMI, body mass index; [c] AJCC, American Joint Commission on Cancer; [d] CEA, carcinoembryonic antigen.

Pathologic response

Although 2 patients did not receive surgical tumor resection, 1 patient sustained advanced 3 synchronous colon cancer on the cecum and ascending and sigmoid colon. Eight specimens demonstrated no viable cancer cells on the primary site (pT0). Nineteen (52.8%)

Table 2. Summary of neoadjuvant radiotherapy (N = 33)

Radiotherapy (dose/fractions)	
45 Gy/25	8 (24.24%)
46.8 Gy/26	3 (9.09%)
50 Gy/25	18 (54.54%)
50.4 Gy/28	4 (12.12%)
RT technique[a]	
Tomo[b]	10 (30.3%)
RA[c]	15 (45.5%)
VMAT[d]	4 (12.8%)
3D-CRT[e]	4 (12.8%)
RT duration (days, median) (range)	35.0 (32-49)
RT-surgery interval[f] days (median) (range)	78.0 (41-164)

[a] RT: radiotherapy; [b] Tomo: helical tomotherapy; [c] RA: rapid Arc; [d] VAMT: volumetric-modulated arc therapy; [e] 3D-CRT: three-dimensional conformal radiotherapy; [f] RT-surgery interval: the period between RT completion and surgery.

specimens demonstrated serosa invasion microscopically (pT3), and 5 presented tumor invasion to extracolonic organs (T4a and T4b). In total of 29 (80.6%) patients exhibited a negative lymph node as per pathology reports, including the patient with the clinical stage as T4N0. The median (range) number of lymph nodes retrieved was 11 (3-26). All resection margins were free of tumor, but 3 specimens (8.3%) showed positive CRMs. Microscopically, 29 of 36 (80.6%) specimens showed lymphovascular invasion and 31 of 36 (86.1%) showed perineural invasion. Most tumors were well differentiated (77.8%), and moderate and poorly differentiated tumors were 16.7% and 5.6% respectively.

Major regression (TRG 1) and moderate regression (TRG 2) were achieved in 9 specimens (25.0%), and 8(22.2%) specimens achieved a pathological complete response (TRG 0). However, 10 specimens (27.8%) showed poor tumor regression, which included 3 synchronous colon cancers in the same patient. A total of 23 specimens (63.9%) represented tumor downstaging to T0-2, and 12 specimens (33.3%) were stable; 31 specimens (86.1%) achieved N downstaging, and 3 specimens (8.3%) revealed the stable N stage. Only 2 specimens showed a poor response to neoadjuvant therapy, and 1 of them had both T and N stage progressed. The synchronous tumor on the sigmoid colon showed a stable T but progressed N stage. In other words, for synchronous tumors, 2 were downstaged, and 1 was progressed in the same patient. Considering the combined T and N stages together, 30 specimens (83.3%) presented TN downstaging. The pathologic evaluation of primary tumor after neoadjuvant CCRT is summarized in Table 3.

CCRT toxicity

Among all the AEs of CCRT, leukopenia was the most common in 31 of 36 (86.1%) patients, but most events are mild to moderate in 26 of 36 patients (72.2%). Anemia was the second leading AEs in 29 of 36 patients (80.5%). For non-hematologic toxicity, fatigue was the leading side effect but all patients exhibited grade1 (72.2%). Approximately half of the patients exhibited gastrointestinal discomfort such as nausea (52.8%) or diarrhea (55.5%). Vomiting was relatively uncommon (25%). Grade1 and 2 peripheral neuropathy and paresthesia often occur (55.5%) but

Table 3. Pathological results and tumor response to neoadjuvant treatment (N = 36)

	No. (%)
ypT	
0	8 (22.2)
1	0 (0)
2	4 (11.1)
3	19 (52.8)
4a	3 (8.3)
4b	2 (5.6)
ypN	
0	29 (80.6)
1	5 (13.9)
2	2 (5.6)
Circumferential resection margin (CRM)	
Negative	33 (91.7)
Positive	3 (8.3)
Lymphovascular invasion	
Yes	29 (80.6)
No	7 (19.4)
Perineural invasion	
Yes	31 (86.1)
No	5 (13.9)
Tumor differentiation	
Well	28 (77.8)
Moderate	6 (16.7)
Poorly	2 (5.6)
Pathologic complete response	
Yes	8 (22.2)
No	28 (77.8)
Tumor regression grade	
0	8 (22.2)
1	9 (25.0)
2	9 (25.0)
3	10 (27.8)
Pathologic T stage	
Downstaging	23 (63.9)
Stable	12 (33.3)
Progressive	1 (2.8)
Pathologic N stage	
Downstaging	31 (86.1)
Stable	3 (8.3)
Progressive	2 (5.6)
Pathologic TN stage	
Downstaging	30 (83.3)
Stable	4 (11.1)
Progressive	2 (5.6)

can usually be corrected by symptomatic treatment. The acute AEs during neoadjuvant CCRT are presented in Table 4.

Survival and treatment outcome

The median (range) follow-up period was 36.5 (7-79.7) months. The estimated 5-year OS rate was 66% (Fig. 1A), and the DFS rate was 43% (Fig. 1B). Of the 36 patients, 10 (27.8%) experienced local recurrence, 13 (36.1%) sustained distant metastasis, and 4 concurrently experienced local recurrence and distant metastasis. One patient demonstrated persistent tumor burden without a response. This patient died after treatment for 36.7 months. The metastatic sites included the liver (n = 2), lung (n = 2), peritoneum (n-2), para-aortic lymph nodes (n = 2) and bones (n = 2). There was no obvious leading organ, but 2 patients had multiple metastases during the same period.

In patients with local recurrence, the estimated 3-year survival rate was 51%, but this rapidly decreased to 17% in the fifth year. In patients with distant metastasis, the estimated 3 and 5-year survival rates were 61% and 36%, respectively. Local recurrence and distant metastasis were poor prognostic factors of patients' survival periods (Table 5).

Eight (22.2%) patients demonstrated pCR. The age and gender indicated no obvious dominance. For colon cancer with involvement of other organs, a complete response was difficult to achieve. Only 1 patient with the clinical stage of T4bN2a showed complete tumor regression, and the number of pCR patients were equal for clinical stages IIIB and IIIC. No patient had local recurrence under pCR, but 3 (37.5%) experienced distant metastasis. The estimated 5-year OS rate of pCR patients was 88%, and the DFS rate was 49%. pCR patients had a trend of longer OS and DFS periods, though no statistical significance was observed. (OS: 71.5 vs. 49.7 months, $p = 0.199$; DFS: 59.9 vs. 44.9 months, $p = 0.349$; Fig. 2A and B).

Table 4. Toxicities during neoadjuvant treatment (N = 36)

Toxicity	Grade 1		Grade 2		Grade 3		Total	
	No.	%	No.	%	No.	%	No.	%
Fatigue	26	72.2	0	0	0	0	26	72.2
Hematologic								
Anemia	13	36.1	11	30.5	6	16.7	29	80.5
Leukopenia	6	16.7	20	55.5	5	13.9	31	86.1
Gastrointestinal								
Nausea	12	33.3	6	16.7	1	2.8	19	52.8
Vomiting	4	11.1	5	13.9	0	0	9	25.0
Diarrhea	12	33.3	7	19.4	1	2.8	20	55.5
Paresthesia	13	36.1	7	19.4	0	0	20	55.5
Oral mucositis	6	16.7	3	8.3	0	0	9	25.0
Dermatitis	9	0.25	2	5.5	0	0	11	30.5

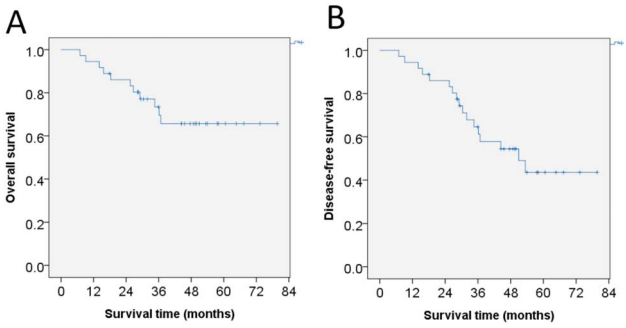

Fig. 1. (A) The overall survival (OS) curve of patients with LACC. The estimated 5-year OS rate was 66%. The median survival period was 60.7 months. (B) The disease-free survival curve of patients with LACC. The estimated 5-year disease-free survival rate was 43%. The median disease survival period was 51.0 months.

Discussion

Adequate surgical resection for LACC is a challenge. The invasion of the tumor to the surrounding organ or extensive lymph node metastasis caused positive resection margin and mad radical resection diffi-

Table 5. Binary logistic regression analysis to predict on LACC patient survival

	Number (%)	Odds ratio (95% CI)	*p* value
pT downstage	23 (63.9%)	1.016 (0.232-4.441)	0.983
pN downstage	31 (86.1%)	4.312 (0.606-30.669)	0.144
pTN downstage	30 (83.3%)	2.750 (0.458-16.525)	0.269
ypN0	29 (80.6%)	4.190 (0.749-23.442)	0.103
pCR[a]	8 (22.2%)	3.889 (0.417-36.287)	0.233
LR[b]	10 (27.8%)	0.159 (0.032-0.784)	0.024
DM[c]	13 (36.1%)	0.180 (0.039-0.836)	0.029

[a] pCR: pathologic complete response; [b] LR: local recurrence; [c] DM: distant metastasis.

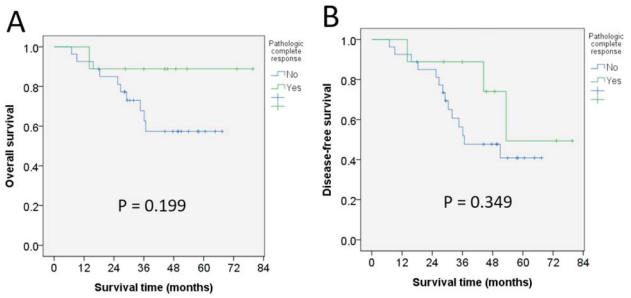

Fig. 2. (A) The 5-year overall survival (OS) curve of patients with and without a pathological complete response. For pCR patients, the estimated 5-year OS rate was 88%. The median survival period was 71.5 months. pCR patients exhibited had a trend of longer OS periods, though no statistical significance (p = 0.199) was observed. (B) The 5-year disease-free survival (DFS) curve of patients with and without pCR. For pCR patients, the estimated 5-year DFS rate was 49%. The median disease survival period was 59.9 months. pCR patients exhibited had a trend of longer DFS periods, though no statistical significance (p = 0.349) was observed.

cult sometimes; this induced subsequent complication and let to patients' mortality. This study collected our treatment experience of LACC with median follow-up time as 36.5 months longest follow-up time as 79.7 months. The data demonstrated that multimodality therapy is a feasible method for LACC treatment. CCRT caused tumor downstaging and few technical surgical difficulties. Approximately 22.2% patients even achieved a pCR and subsequent better outcomes. The degree of toxicity is usually acceptable and can be relieved by medicines. These data suggest that neoadjuvant CCRT is an alternative strategy for LACC compared with direct wide surgical resection followed by adjuvant therapy.

Consistent with our results, evidence has indicated that nodal involvement is a major predictor of oncologic outcomes in patients with CRC.[14,15] Twenty-nine (80.6%) specimens showed no lymph node invasion (pN0). For pN0 patients, the estimated 5-year OS and DFS rates were 73% and 49% respectively. The median survival period was 64.2 months and the median disease survival period was 55.8 months (Fig. 3A and B). pN downstaging rate was 86.1%. Binary logistic regression analysis revealed that N downstaging is related to patients' survival, but no statistical significance (OR: 4.312, p = 0.144) was observed. Additionally, no lymph node invasion is also related to patients' survival, but without statistical significance (OR: 4.190, p = 0.103). Approximately 63.9% of our patients showed pT downstaging, but this factor had no value to predict patients' survival (OR: 1.016, p = 0.983). Patients with ypT0 all showed negative lymph node invasion. These results are possibly attributable to the marked influence of neoadjuvant CCRT. For locally advanced rectal cancer, neoadjuvant CCRT has been associated with nodal downstaging and a decrease in the pathologic lymph node harvest.[16,17] Our findings reveal a similar effect of neoadjuvant CCRT on eradication of lymph node metastasis in LACC.

Neoadjuvanct CCRT for LACC tumor downstaging followed by surgical resection has been well demonstrated, and a pCR after neoadjuvant CCRT has been proved to be a major predictor of tumor control and patients' survival.[18] Some research reported that oxaliplatin can improve the pCR rate.[19-23] Extending the course of neoadjuvant FOLFOX therapy before the surgery was also thought to be a feasible way to enhance pCR rates.[24] The FOWARC trial demonstrated that FOLFOX chemotherapy administered concurrently with and following radiotherapy resulted

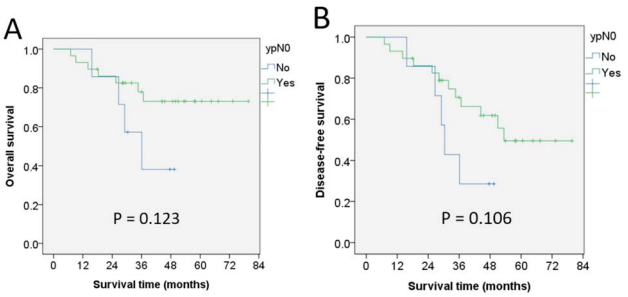

Fig. 3. (A) The 5-year overall survival (OS) curve of patients with and without pN0. For pN0 patients, the estimated 5-year OS rate was 73%. The median survival period was 64.2 months. pN0 patients exhibited had a trend of longer OS periods, though no statistical significance (p = 0.123) was observed. (B) The 5-year disease-free survival curve of patients with and without pN0. For pN0 patients, the estimated 5-year disease-free survival rate was 49%. The median disease survival period was 55.8 months. pN0 patients had a trend of longer DFS periods, though no statistical significance (p = 0.106) was observed.

in a higher pCR rate than fluorouracil-based CCRT or perioperative FOLFOX alone.[4] Our prior study also showed similar results to the FOWARC trial.[25] Nevertheless, our treatment strategy on LACC has not been well documented on LACC.

A Canadian group reported that of 33 patients with LACC who were treated with neoadjuvant concurrent 5-FU and radiotherapy, only 1 patient (3%) achieved a pCR.[26] The FOxTROT trial assessed the role of neoadjuvant chemotherapy in LACC management by evaluating the efficacy and safety of preoperative FOLFOX-based chemotherapy in a randomized controlled manner; 2 patients (2%) from the neoadjuvant group achieved a pCRs.[27] Furthermore, a phase II trial demonstrated that 3 (4.2%) of the71 operated patients achieved a pCR after 3 cycles of neoadjuvant XELOX [capecitabine (2000 mg/m^2) orally administered on days 1-14 (q3w), and oxaliplatin (130 mg/m^2) intravenously infused on day 1 (q3w)].[28] Arredondo et al. investigated 65 patients with LACC treated with either neoadjuvant XELOX or FOLFOX-based chemotherapy; 3 (4.6%) patients achieved a pCR.[29] This study reported a higher pCR rate (22.2%) than previous studies reporting a pCR rate of approximately 2%-4%. Patients achieving a pCR had a higher chance to survive with odds ratio as 4.706; however, it did not reach significance (Table 5). Similarly, in 2018, Chang et al. collected 60 patients with LACC and demonstrated that the pCR rate was 26.3%. The OS rate for pCR patients was 95.2% after following up for 42 months. The authors found that 30% of patients sustained distant metastasis after tumor resection, and they thought distant metastasis is a major cause of treatment failure.[30] In the present study, the local recurrence rate for pCR patients was 0, but 3 patients (37.5%) sustained distant metastasis after the surgery. One patient of the distant metastasis group died 14.1 months after initial diagnosis because of multiple metastases. The other 2 patients survived for 53.4 and 44.4 months, respectively, under regular chemo- and target therapy. Only 1 death occurred in our 8 patients achieved a pCR, and the 5-year OS rate of pCR patient was 88%.

Neoadjuvant CCRT is the optimal treatment in patients with locally advanced rectal cancer.[4] Although several studies have reported promising results for neoadjuvant chemotherapy, we used an intensified multimodality approach that combines chemotherapy and radiotherapy in patients with LACC, particularly in those with clinical T4 tumors. The prognosis of a T4 colon cancer is the worst, and T4 tumors have been closely associated with an involved resection margin.[31,32] However, Chang et al. demonstrated an adequate response on T4b patients with the R0 resection rate of 77.1% and the OS rate of 74.3%.[30] In the present study, 24 (63.2%) patients were initially diagnosed with the T4 stage. After neoadjuvant CCRT and surgical resection, pathologic features revealed only 3 patients (8.33%) with the pT4a stage and 2 patients (5.55%) with the pT4b stage. Among these 5 pathologic T4 patients, 2 exhibited a positive circumferential margin, 1 sustained distant metastasis, and they died with an average survival period 19.7 months after diagnosis. However, considering the obvious response rate between clinical and pathological stage, neoadjuvant CCRT should be the feasible alternative treatment for LACC.

R0 resection is a key point to evaluate the prognosis of colon cancer treatment. A positive resection margin as R1 or R2 resection indicates cancer recurrence and a disappointed survival rate. Cukier et al. analyzed the oncologic outcomes of neoadjuvant CCRT followed by multivisceral resection for primary LACC and reported a R0 resection rate of 100%, with a postoperative complication rate of 36% and 0% surgical mortality.[26] Qiu et al. found that neoadjuvant CCRT can effectively reduce peripheral tumor infiltration and thereby decrease the necessity for multivisceral resection. Therefore, neoadjuvant CCRT may reduce postoperative complications caused by multivisceral resection.[33] In the present study, all patients who received surgical resection got R0 resection, and the unfavorable margin only occurred on the tumor circumference. This result suggests that neoadjuvant CCRT is feasible for tumor downstaging and therefore reduces surgical technique difficulty and complications. In our previous study, neoadjuvant CCRT followed by radical resection did not increase the postoperative complication rate compared with resection alone. The overall postoperative complication rate

was 14.7%. The rate of anastomosis leakage was 2.9%. In total, 5.88% patients sustained severe ileus and required surgical intervention.[34] However, 63.9% patients required ileostomy or colostomy for bowel decompression before CCRT, of which 2-stage or multistage surgeries are necessary for LACC treatment.

The eligibility criterion of patients with LACC suitable for a neoadjuvant CCRT remains debatable. Chang et al. applied neoadjuvant CCRT for patient with clinical stage T4b or unresectable tumor found during the operation.[30] In our study, we chose T3 tumor with extramural extension of > 5 mm or a T4 tumor diagnosed using imaging studies. In this way, the accuracy of CT image diagnosis is essential for appropriate treatment. Precise evaluation of lymph node metastasis was difficult as observed on current CT image; instead, numerous studies have demonstrated that CT can identify T3 tumors with extramural extension or T4 tumors.[21,29,35]

Although neoadjuvant CCRT showed effective response on LACC treatment, many patients experienced obvious AEs. Cukier et al. reported that 9% of the patients with LACC experienced Grade 3 or higher grades of AEs during 5-FU-based CCRT.[26] In the present study, oxaliplatin and 5-FU were used in the neoadjuvant setting to maximize the effect of CCRT on LACC, but adverse effects were relatively tolerable. In our previous studies or in other studies investigating the influence of FOLFOX-based CCRT in patients with rectal cancer, Grades 3 and 4 AEs ranged from 24% to 40%.[16,34,36] However, in the current study, the occurrence rate was 13%-16% in Grades 3 and 4 AEs. Approximately 76.6% of the patients received intensity-modulated radiotherapy with either RA or tomotherapy, which might partly contribute to the improved toxicity profiles because of normal organ sparing.[36] The most common AEs are hematologic events and can be manageable.

The present study has some limitations. First, although the median follow-up time was 36.5 months, the collected patient number is relatively small. Second, this was a retrospective study; therefore, sampling may have been affected by selection bias. Third, postoperative chemotherapy regimens were varied in our study, which might contribute to disease control and survival.

Conclusion

Our study presents that neoadjuvant CCRT is an effective and safe treatment strategy for LACC. With modern radiotherapy equipment and chemotherapy agents, not only R0 resection but also pCR rates can reach a higher level; hence, they can improve patients' outcome and survival. Even with pCR condition, distant metastasis risk remains. As a result, aggressive follow-up is necessary. A longer follow-up time or a prospective, randomized control study may be required to validate our results.

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原　著

對於侵犯性大腸直腸癌使用術前同步化學放射治療之長期追蹤

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目的　侵犯性大腸癌的治療至今仍是一項挑戰，患者的預後多不甚理想。然而使用術前同步化學放射治療，有機會提高腫瘤切除率並提升存活率，本研究旨在探究術前同步化學放射治療之療效、毒性、病理反應和長期存活時間。

方法　我們收入了 36 名，在 2012 年 1 月至 2017 年 1 月被診斷為侵犯性大腸癌的患者，藉由回溯病歷資料，分析其治療成果和治療細節，所有的患者都接受了術前同步化學放射治療，化學治療所使用的藥物包括了奧沙利鉑，亞葉酸和 5-氟尿嘧啶，即所謂的 FOLFOX。

結果　T 和 N 降階的比率分別是 63.9% 和 86.1%。貧血是最常見的三級不良反應 (18.89%)，其次是白血球低下 (16.67%)。絕大多數的不良反應都可以用藥物控制症狀。在 36 名患者中，有 34 名在同步化學放射治療後，順利接受手術切除腫瘤，2 名患者腫瘤仍無法切除。有一名患者同時有 3 顆侵犯性大腸癌，並成功手術切除。8 名患者 (22.2%) 達到完全病理反應。羅吉斯迴歸分析發現局部復發和遠端轉移是兩項不利於存活的預測因子。整體 5 年存活率為 66%，無疾病存活率為 43%。病理完全反應和無淋巴結侵犯的患者有較長的整體存活率和無疾病存活率，但均未達統計學意義。在病理完全反應的患者，局部復發率為 0，但有 3 名患者 (37.5%) 出現遠端轉移。

結論　我們的研究成果顯示術前同步化學放射治療，可以安全地使用在侵犯性大腸癌的患者身上，達到治療效果。有病理完全反應和無淋巴結侵犯的患者，其存活時間較長。對於病理完全反應的患者，沒有觀察到局部復發，但有機會出現遠端轉移。

關鍵詞　侵犯性大腸癌、同步化學放射治療、長期追蹤。