Original Article

Neoadjuvant Short-course Radiotherapy or Concurrent Chemoradiotherapy Followed by Radical Colectomy in Locally Advanced Colon Cancer Patients

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Key Words
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Purpose. Locally advanced colon cancer (LACC) is usually defined as having a large tumor size, infiltrating tumor, or adhering to adjacent structures. Frequently, LACC should be considered as having an oncologically unresectable status. Neoadjuvant short-course radiotherapy (SCRT) or concurrent chemoradiotherapy (CCRT) has could be a choice for locally advanced rectal cancer. However, the role of neoadjuvant SCRT or CCRT in the treatment of LACC remains unclear. The aim of this study was to analyze neoadjuvant SCRT or CCRT outcome in LACC patients.
Methods. We retrospectively reviewed LACC patients from our institutional database between January 2008 to December 2018. Patients' demographic data, radiotherapy (RT) toxicity, surgical results, pathologic outcomes following SCRT or CCRT, 5-year overall survival (OS) rates and disease-free survival (DFS) rates were collected for analysis.
Results. A total of 19 patients were enrolled. All patients had a clinical T4a or T4b stage and excluded clinical T3 stage with 14 patients (73.7%) were N2 positive lymph nodes status. There was no toxicity in the SCRT group. For the CCRT group, the major toxicity was gastrointestinal (GI) syndrome, and all seven patients (100%) had a grade 1-2 adverse effect. A multivisceral resections were required in seven patients (35.8%). R0 resection was 78.9%, pathologic complete response (pCR) rate was 5.3%, and local recurrence rate was 5.3% in stage III patients. The 5-year OS and DFS were 91.7% and 83.3% in stage III patients, respectively.
Conclusions. Our study demonstrates that neoadjuvant SCRT or CCRT followed by radical colectomy are feasible and safe treatment in LACC patients.
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Most primary colorectal neoplasms worldwide are adenocarcinomas. Radical surgical resection is the standard therapeutic procedure for stage I to III colon cancer according clinical practical guideline.[1] For stage IV colon cancer, primary cancer resection is also an important part of the procedure based on multidisciplinary guidelines.[2]

The term, locally advanced colon cancer (LACC), is usually defined as having a large tumor size, infiltrating tumor, or adhering to adjacent structures. Fre-

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quently, LACC should be considered as having an oncologically unresectable difficult status and represents 5% to 22% of all colorectal carcinomas.[3,4] The radical resection margin (R0) of colon cancer are very important prognostic factors for patients' survival. However, the R0 resection rate is much lower in LACC. The positive resection margin rate can be as high as 20% (ten of 50) in LACC patients.[5] LACC is associated with higher risks of a positive resection margin, higher local recurrence rates, inferior overall survival (OS) rate, and poor disease-free survival (DFS) rate.[6] Patients with an R1 or R2 resection have a 0% 5-year survival rate, compared with 80.7% in R0 resection patients in Croner's prospective study.[7] And, the total 5-year OS rates in all stage IIIB and IIIC colon cancer were 46% and 28% based on the expanded Surveillance, Epidemiology, and End Results (SEER) database.[8]

For aggressive LACC treatment, neoadjuvant chemotherapy alone, postoperative adjuvant chemoradiotherapy (CRT), neoadjuvant short-course radiotherapy (SCRT), or concurrent chemoradiotherapy (CCRT) may be an alternative treatment strategy to improve patient survival rates. The FOxTROT study was the first randomized controlled trial (RCT) of neoadjuvant chemotherapy for LACC. Neoadjuvant chemotherapy resulted in significant downstaging of TNM status and reduced resection margin involvement with acceptable toxicity.[5] The postoperative adjuvant radiotherapy (RT) or CRT could improve OS in some selective patients with both pT4 and positive resection margin from the American National Cancer Database (NCDB).[9]

The neoadjuvant SCRT or CCRT have already become standard treatment for locally advanced rectal cancer since it can improve the oncological outcomes.[10-13] However, the role of neoadjuvant SCRT or CCRT in the treatment of LACC remains unclear. Until now, few studies with a small number of patients have limited evidence.[6,14-17] Based on the rectal cancer study, the neoadjuvant CCRT was superior to postoperative adjuvant CRT with improved local control rates and reduced toxicities.[10,18]

For the present study, we hypothesized that neoadjuvant SCRT or CCRT would increase radical R0 resection rate, pathologic complete response (pCR) rate, OS rate, and decrease local recurrence. We retrospectively reviewed our single institutional database for these short-term outcome analyses to validate our hypothesis.

Material and Methods

We retrospectively reviewed colorectal carcinoma database between January 2008 to December 2018 at our institution. Patients who were diagnosed as LACC and underwent neoadjuvant SCRT or CCRT were recruited into the study. LACC was defined as potentially incomplete radical resection, such as large tumor size, aggressive behavior, and T3 stage with ≥ 5 mm tumor invasion beyond muscularis propria or T4 tumor by CT image studies. Rectal cancer within a 15 cm level from the anal verge was excluded. Other exclusion criteria were palliative RT without radical resection, Eastern Cooperative Oncology Group (ECOG) score > 2, or multiple medical comorbidities.

Neoadjuvant SCRT or CCRT

Patient files were retrospectively analyzed, including demographic data, oncologic status, SCRT regimens, CCRT regimens, palliative chemotherapy regimens with or without biological reagents, surgical outcomes, pathologic results, and related adverse effects. The radiation dose of SCRT was 25 Gy delivered in five fractions. The total radiation dose of CCRT was 45-50.4 Gy delivered in 25-28 fractions.

For stage III LACC patients, the neoadjuvant chemotherapy was administered according to clinical consideration, and the regimens were 5-Fluorouracil/leucovorin (5-Fu), or Tegafur (UFUR), or folinic acid, fluorouracil, and oxaliplatin (FOLFOX) regimens. For stage IV LACC patients, palliative chemotherapy with or without biological agents was administered based on all-RAS and BRAF analysis results.

RT responses, toxicities, surgical, and pathologic results

The en bloc colectomy with lymph node dissection was performed after neoadjuvant treatment. While cancer infiltration of dense adhesion to adjacent or-

gans existed, the multivisceral resection would be rendered. The primary endpoints were the R0 resection rate, clear circumferential resection margin (CRM) rate, and pCR rate. The secondary endpoints were the local recurrence rate, RT toxicities, tumor regression grade (TGR), tumor downstaging rate, and nodal downstaging rate. Binominal data were presented as proportions, and continuous data were reported as medians and ranges.

Survival analysis and statistical methods

OS was defined as the date from the starting SCRT or CCRT until any cause of death up to five years of follow-up, and the DFS was defined as the date from the starting SCRT or CCRT until any type of recurrence since the last follow-up date. OS and DFS rates were calculated with the Kaplan-Meier method. All analyses were performed using IBM SPSS software, Version 22.0.

Results

Patient demographics

A total of 19 patients were enrolled in the analysis. The median age was 62 years old (range, 36-83 years), and 10 patients were male (52.2%). There were 8 patients (42.1%) with right-sided colon cancer and 11 patients (57.9%) with left-sided colon cancer. Most cancers were located in the sigmoid colon (42.1%), followed by the ascending colon (26.3%). All patients had a clinical T stage of T4a or T4b and 14 patients (73.7%) were N2-positive lymph nodes status. Six patients (31.6%) were stage IV LACC. Treatment by SCRT, or CCRT, were assigned based on the clinical condition and physician's consideration. Among those, 12 patients (63.2%) received the SCRT regimen. The preoperative and postoperative chemotherapy regimens are listed in Table 1.

Surgical results

Five patients (26.3%) performed diverting entero-

Table 1. Patients' demographic data (n = 19)

	n	%
Age, median (years, range)*	62	(36-83)
Gender		
Male	10	52.2
Female	9	47.8
BMI, median (kg/m^2, range)*	23.5	(19.2-32.4)
Tumor location		
Right side colon	8	42.1
Ascending colon	5	26.3
Hepatic flexure colon	2	10.5
Transverse colon	1	5.3
Left side colon	11	57.9
Descending colon	3	15.8
Sigmoid colon	8	42.1
Clinical tumor T stage		
T3a/T3b	0	0
T4a	8	42.1
T4b	11	57.9
Clinical tumor N stage		
N0	0	0
N1a/N1b	2	10.5
N1b	3	15.8
N2a/N2b	3	15.8
N2b	11	57.9
Clinical tumor M stage		
M0	13	68.4
M1a	3	15.8
M1b	2	10.5
M1c	1	5.3
AJCC staging		
II	0	0
IIIa	0	0
IIIb	3	15.8
IIIc	9	47.4
IVa	3	15.8
IVb	3	15.8
IVc	1	5.3
Pretherapeutic CEA level		
< 5 ng/ml	11	57.9
> 5 ng/ml	8	42.1
RT regimen (dose/fractions)		
SCRT, 2500 cGy/5 fr	12	63.2
CCRT, 4500-5040 cGy/25-28 fr	7	36.8
RT-surgery interval day, median (days, range)*		
SCRT, n = 12*	28	(3-162)
CCRT, n = 7*	43	(31-92)
Neoadjuvant or palliative chemotherapy regimens		
SCRT, n = 12		
FOLFOX	1	5.3

Table 1. Continued

	n	%
Bevacizumab + FOLFIRI	1	5.3
Panitumumab + FOLFIRI	3	15.8
None	7	36.8
CCRT, n = 7		
5Fu	2	10.5
UFUR	2	10.5
FOLFOX	3	15.8
Post-op chemotherapy regimens		
5Fu	0	0
UFUR	3	15.8
FOLFOX	9	47.4
Bevacizumab + FOLFIRI	2	10.5
Panitumumab + FOLFIRI	2	10.5
Cetuximab + FOLFIRI	1	5.3
None	1	5.3

* Median (range).
BMI, body mass index; AJCC, American Joint Committee on Cancer; CEA, carcinoembryonic antigen; RT, radiotherapy; SCRT, short-course radiotherapy; CCRT, neoadjuvant concurrent chemoradiotherapy; FOLFORI, Folinic acid, fluorouracil, and irinotecan; FOLFOX, Folinic acid, fluorouracil, and oxaliplatin; UFUR, tegafur-uracil.

stomy, and one patient (5.3%) performed self-expanding metal stent (SEMS) before neoadjuvant therapy owing to clinical obstructive symptoms. All six patients with obstruction were located in left-side colon. The other thirteen patients, three patients (23.1%) of them performed postoperative enterostomy. One of the three patients (33%) was right-sided colon cancer, and the other two patients (66.7%) were left-sided colon cancer. The median tumor downing size percentage was 71.4%. Nine of the 19 LACC patients (47.4%) could receive minimal invasive surgery (MIS), including the one patient that received reduced port da-Vinci robotic surgery. Multivisceral resection was required in seven patients (35.8%) (Table 2).

RT toxicity analysis

Table 3 shows the neoadjuvant RT toxicity. There is no RT-related toxicity in the SCRT group. For the CCRT group, the major toxicity is gastrointestinal (GI) syndrome, and all seven patients (100%) had grade 1-2 adverse effects. Grade 1-2 skin toxicity was

Table 2. Surgical outcomes in LACC patients

	n	%
Pretherapeutic colonic decompression		
Enterostomal creation		
Right side colon	0	0
Left side colon	5	26.3
SEMS insertion		
Right side colon	0	0
Left side colon	1	5.3
No colonic decompression		
Right side colon	8	42.1
Left side colon	5	26.3
Post-OP enterostomal creation, n = 13		
Enterostomal creation[#]		
Right side colon[#]	1	7.7
Left side colon[#]	2	15.4
No enterostomal creation[#]		
Right side colon[#]	7	53.8
Left side colon[#]	3	23.1
Tumor downing size, median (percentage, range)*,[##]	71.4%	(11%-100%)
MIS or open surgery		
MIS		
Laparoscopic surgery	8	42.1
da Vinci robotic surgery	1	5.3
Open surgery	10	52.6
Multivisceral resection	7	36.8
Local recurrence	1	5.3

[#] Exclude pretherapeutic colonic decompression, n = 13.
* Median (range).
[##] Compare pretherapeutic clinical tumor size and postoperative pathologic tumor size.
LACC, locally advanced colon cancer; SEMS, self-expanding metal stent; Post-OP, postoperative; MIS, minimal invasive surgery.

Table 3. SCRT and CCRT toxicities

	n	%
RT toxicities		
SCRT, n = 12		
GI syndrome	0	0
Skin reaction	0	0
Genitourinary toxicity	0	0
CCRT, n = 7		
GI syndrome, n = 7		
Grade 0	0	0
Grade 1-2	7	100
Grade 3-4	0	0
Skin reaction, n = 7		
Grade 0	3	42.9
Grade 1-2	4	57.1
Grade 3-4	0	0
Genitourinary toxicity, n = 7		
Grade 0	0	0
Grade 1-2	0	0
Grade 3-4	0	0

SCRT, short-course radiotherapy; CCRT, neoadjuvant concurrent chemoradiotherapy; RT, radiotherapy.

57.1% without grade 3-4 toxicity. Genitourinary toxicity did not occur.

Pathologic outcomes after neoadjuvant SCRT or CCRT

The pathologic outcomes after radical resection surgery as Table 4 shown. The pathologic data revealed that only one patient (5.3%) achieved ypT0, two (10.5%) of ypT2, nine (47.4%) of ypT3, and still seven (36.8%) without tumor downstaging. Eleven patients (57.9%) achieved ypN0 without malignant lymph nodes invasion. The median harvested lymph nodes were 19 (range, 2-70 nodes). Eight patients had positive lymph nodes (range, 0-8 nodes). Four (21.1%) patients had extranodal involvement, two (10.5%) had perineural invasion, and one (5.3%) had lymphovascular invasion. Two patients (10.5%) had well differentiation-differentiated histology, six (31.6%) had moderate differentiation, nine (47.4%) had poor differentiation, and two (10.5%) had mucinous differentiation. Grade 0 TGR (complete response), grade 1 TGR (moderate response), grade 2 TGR (minimal response), and grade 3 TGR (poor response) were achieved in one (5.3%), 11 (57.9%), five (26.3%), and two (10.5%) patients, respectively. Four patients (21.1%) had a positive CRM or less than 1 mm CRM. The R0 resection rate was 78.9%. Only one patient (5.3%) achieved a pCR in our study. A comparison between the pretherapeutic clinical TN stage and postoperative pathologic TN stage indicated that 12 (63.2%) patients had T-downstaging, 17 (89.5) had N-downstaging, and 18 (94.7%) had TN-downstaging. Table 5 presents the status of TN-downstaging. These results show that the clinical T4a cases had good downstaging between ypT0 to ypT3. Nevertheless, seven of eleven (63.6%) cT4b patients still had ypT4 status without T-downstaging.

Survival data

The median follow-up period was 26.9 months (range, 9.73-60 months). The 5-year OS rate was 91.7% in stage III patients and 33.3% in stage IV patients, respectively. The 5-year DFS rate was 83.3% in stage III patients (Fig. 1). There were three recurrences in stage III patients; two patients had distant metastasis within

Table 4. Postoperative pathologic results (n = 19)

	n	%
ypT stage		
0	1	5.3
1	0	0
2	2	10.5
3	9	47.4
4	7	36.8
ypN stage		
0	11	57.9
1	6	31.6
2	2	11.5
Harvest lymph nodes, median (n, range)*	19	(2-70)
Metastatic lymph nodes, median (n, range)*	0	(0-8)
Extranodal involvement	4	21.1
Perineural invasion	2	10.5
Lymphovascular invasion	1	5.3
Tumor differentiation		
Well differentiation	2	10.5
Moderate differentiation	6	31.6
Poor differentiation	9	47.4
Mucinous differentiation	2	10.5
Tumor regression grade		
Grade 0, complete response	1	5.3
Grade 1, moderate response	11	57.9
Grade 2, minimal response	5	26.3
Grade 3, poor response	2	10.5
CRM		
Positive margin or free margin < 1 mm	4	21.1
Negative margin	15	78.9
pCR		
Complete	1	5.3
Incomplete	18	94.7
Pathologic T stage status		
Downstaging	12	63.2
Stable	7	36.8
Progression	0	0
Pathologic N stage status		
Downstaging	17	89.5
Stable	2	10.5
Progression	0	0
Pathologic TN stage status		
Downstaging	18	94.7
Stable	1	5.3
Progression	0	0

* Median (range).
CRM, circumferential resection margin; pCR, pathologic complete response.

Table 5. Comparison of clinical stage to pathologic T and N stage (n = 19)

Clinical stage	Pathologic T stage						Pathologic N stage		Total
	ypT0	ypT1	ypT2	ypT3	ypT4a	ypT4b	ypN negative	ypN positive	
cT4a	1 (5.3)	0 (0)	1 (5.3)	6 (31.6)	0 (0)	0 (0)	-	-	8 (42.1)
cT4b	0	0 (0)	1 (5.3)	3 (15.8)	1 (5.3)	6 (31.6)	-	-	11 (57.9)
cN negative	-	-	-	-	-	-	0 (0)	0 (0)	0 (0)
cN positive	-	-	-	-	-	-	11 (57.9)	8 (42.1)	19 (100)
Total	1 (5.3)	0 (0)	2 (10.5)	9 (47.4)	1 (5.3)	6 (31.6)	11 (57.9)	8 (42.1)	19 (100)

Data are presented as n (%).

five years. One had peritoneal carcinomatosis after 10 years of surgery. Hence, the local recurrence was 5.3% in our serial study.

Discussion

This study presented the pathologic outcomes and survival rates of neoadjuvant SCRT or CCRT followed by radical colectomy in LACC patients at a single institutional hospital. We have relatively good R0 resection, low local recurrence rate, better 5-year OS rate, and acceptable pCR rate. The R0 resection rate was 78.9%. The local recurrence rate was 5.3%. The 5-year OS rates were reported as 91.7% and 33.3% for stage III and stage IV patients, respectively. The incidence rates of RT toxicities, postoperative complications, and postoperative new enterostomal creation were low. The SCRT group had no RT-related toxicity, and the CCRT group had some RT-related toxicity, 100% grade 1 GI toxicity and 57.1% grade 1 to 2 skin toxicity. The postoperative temporary enterostomal creation rate was 23.3% and 13 patients had not a pretherapeutic enterostomy. In addition, as high as 47.4% of patients received MIS successfully. The operative complication was low without 30 days of mortality. Based on our study, we suggested that neoadjuvant SCRT or CCRT followed by radical colectomy in LACC patients might be an alternative therapeutic option to improve the patient's oncological outcome.

From the serial literature reviewed, we know that the surgical management of LACC remains a challenge because these lesions usually extend into surrounding organs or structures. Margin-free radial resection can achieve low local recurrence, good long-term survival, and usually need multivisceral organ en bloc resection in most cases, reported by Landmann et

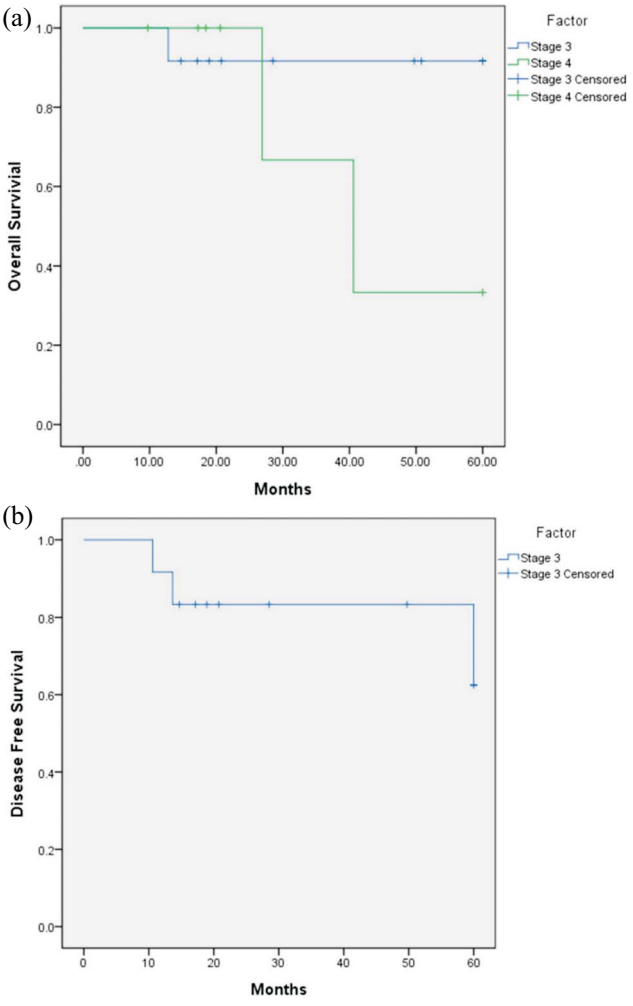

Fig. 1. Overall survival rate and disease-free survival rate. (a) Stage III and stage IV overall survival rate and (b) Disease-free survival rate in locally advanced colon cancer patients receiving neoadjuvant short-course radiotherapy or concurrent chemoradiation therapy and radical colectomy.

al.[19] Lehnert et al. reported that R0 resection was the important predictor of survival, and the 5-year OS rate was 69%, 36%, and 13% for stage II, III, and IV cases, respectively.[20] Nishikawa et al. also found that R0 resection improved the prognosis in LACC invasion of adjacent organs after neoadjuvant treatment, and multivisceral resection were also acceptable morbidity and minimal mortality.[21] However, the R0 resection rate was lower in LACC, reported by the FOxTROT study.[5] Such a dilemma may be the prominent large tumor size, adjacent organs, or structure invasion, and lead to incomplete resection. Hence, neoadjuvant therapies would be important before surgery to make tumor size shrinkage, downing pathologic tumor stage, and pursuit to raise R0 resection rate.

The greater efficacy of neoadjuvant SCRT or CCRT has been well accepted for rectal cancer treatments.[10-13] The better oncologic outcomes and survival rates for patients that achieved pCR following neoadjuvant SCRT or CCRT in rectal cancer were widely recognized from many clinical trials.[22-27] Kuan et al. reported that 259 (13.6%) of 1914 neoadjuvant CCRT rectal cancer patients achieved pCR and had better 5-year OS rates up to 90% than 69% OS rates in non pCR patients from the Taiwan Cancer Registry (TCR) database.[22] The CAO/ARO/AIO-04 phase III RCT study reported that adding oxaliplatin to 5-Fu based neoadjuvant CCRT significantly achieved pCR in 103 (17%) of 591 patients, and improved the 3-year DFS rate up to 75.9% with clinically staged cT3-4 or cN1-2 rectal cancer.[28,29] In summary, we believe that R0 resection and pCR status would improve outcomes and survival rates, whereas neoadjuvant SCRT or CCRT might increase the R0 resection or pCR rate.

However, the role of neoadjuvant SCRT or CCRT in the LACC would be determined. From the literature review, there are only two prospective studies;[15,16] one is a nationwide database study from American NCDB,[17] and two are retrospective studies.[6,14] In 2012, Cukier et al. retrospectively analyzed 33 LACC patients received neoadjuvant 5-Fu based CCRT followed by multivisceral resection and reported a 100% R0 resection rate, 3% pCR rate, and 67% ypT4b disease in 22 of 33 patients. The 3-year OS and DFS rate were 85.9% and 73.7%, respectively.[14] Our study is similar to Cukier's study. In 2016, Qiu et al. prospectively analyzed 21 initially unresectable LACC receiving neoadjuvant CCRT and reported a 95.2% R0 resection rate, 38.1% pCR rate, only a 33.3% multivisceral resection rate in seven patients, and a 95.2% 3-year OS rate. Qiu's study suggested that neoadjuvant CCRT could markedly decrease the need for multivisceral resection by sterilizing the peripheral extent of tumor infiltration, which may help to decrease postoperative morbidity and mortality.[15] The multivisceral resection rate was 36.8% in our study and is similar to Qiu's study results. In 2017, Huang et al. published a prospective study using FOLFOX-based neoadjuvant CCRT to treat 34 LACC patients and reported an R0 resection rate of 91.2%, the highest pCR rate of 26.4% in 9 of 34 patients, a 2-year OS rate of 88.7%, and a 2-year DFS rate of 73.6%. Huang's study showed that neoadjuvant CCRT with FOLFOX regimens would be feasible and safe with high pCR rate and acceptable toxicity.[16] Hawkins et al. presented that neoadjuvant SCRT or CCRT for clinical T4 colon cancer was associated with a superior R0 resection rate and an improved OS from the NCDB database in 2018. Patients with T4b disease may obtain great benefits from neoadjuvant SCRT or CCRT.[17] The postoperative morbidity and mortality were acceptable in the above five studies. Thus, we believe that neoadjuvant SCRT or CCRT is feasible and safe for LACC patients.

Several studies have investigated the efficacy and safety of neoadjuvant chemotherapy for LACC. There was no head-to-head RCT between different neoadjuvant modalities till now. The FOxTROT study was the largest RCT for neoadjuvant chemotherapy and had significant TNM downstaging and low positive resection margin (4%). However, the FOxTROT study only reached a 2% pCR rate in two of 99 patients.[5] These data showed that the neoadjuvant SCRT or CCRT probably has a higher pCR rate than only preoperative neoadjuvant chemotherapy treatment.

Our limited 19-patient datasets would contain some interesting information. In Table 1, all enrolled patients were cT4a (42.1%) and cT4b (57.9%). Clinical T4b cancer means malignant invasion to the adjacent organs and the need of multivisceral resection can usually achieve R0 resection. Our multivisceral resec-

tion rate was 36.8%, and it may benefit from neoadjuvant SCRT or CCRT. In Table 2, 10 (76.9%) of 13 patients had no need of postoperative enterostomal creation. The average downing tumor size was 71.4%. Due to the reduced tumor size from neoadjuvant SCRT or CCRT, the MIS would be performed safely, and 47.4% of patients received laparoscopic or da Vinci robotic surgery. In Table 4, one patient (5.3%) was still ypT4a stage, and six patients (31.6%) were ypT4b stage. The pathologic T-downstaging only reached 63.2%, and these patients were all initially cT4b stage. Patients who were cT4a stage could downstage between ypT0 to ypT3 stage. This study revealed that cT4a stage had better T-downstaging and resumed radical resection more practically. However, the results of T-downstaging in cT4b stage patients were few after SCRT or CCRT and needed more multivisceral resection than cT4a stage. CAO/ARO/AIO-04 showed improved pCR and 3-year DFS with FOLFOX compared with fluorouracil alone.[28,29] The FOLFOX-based chemotherapy may be more effective regimens for neoadjuvant treatments in LACC. Therefore, multimodal therapies, such as aggressive neoadjuvant CCRT with FOLFOX-based chemotherapy, may be used for cT4b patients to get more therapeutic responses.

However, this study had some limitations. First, our pCR rate was only 5.2% in one patient, and the proportion rate was much lower compared with 38.1% in Qiu's study, and 26.4% in Huang's study.[15,16] These two studies were prospective studies, and all enrolled patients were treated with long-course CCRT regimens. The neoadjuvant CCRT has a good pCR rate that ranges from 11.3% to 27.5% from a currently released phase III neoadjuvant CCRT trial in 4700 rectal cancer patients.[28,30-35] Half of LACC patients in our study received neoadjuvant SCRT without combination chemotherapy, and thus a low pCR rate resulted. Besides, many patients were cT4b stage, and these were more locally advanced than cT4a stage resulting in a lower pCR rate than other studies. Second, our study was a retrospective study, among those that were practiced using diverse neoadjuvant RT and chemotherapy regimens. Our results only explained that neoadjuvant SCRT or CCRT were feasible and safe management for LACC, whereas the most effective neoadjuvant treatment regimens could not provide an answer in this study.

Conclusions

Our study demonstrates that neoadjuvant SCRT or CCRT followed by radical colectomy are feasible and safe treatment in LACC patients. There are associated with higher R0 resection rates, TN-downstaging, significant tumor size shrinking, low local recurrence rate, better OS rate, and DFS rate, and acceptable RT toxicity. The MIS provides possible R0 resection for half of elective patients. Such preliminary data also provide the evidence of multimodality treatments for LACC are efficient. Further prospective RCT or head-to-head studies comparing different neoadjuvant regimens are warranted.

References

1. Vogel JD, Eskicioglu C, Weiser MR, Feingold DL, Steele SR. The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the treatment of colon cancer. *Dis Colon Rectum* 2017;60:999-1017.
2. Lan YT, Lin JK, Jiang JK. Effects of a multidisciplinary team on colorectal cancer treatment. *Formos J Surg* 2015;48:145-50.
3. Vieira RA, Lopes A, Almeida PA, Rossi BM, Nakagawa WT, Ferreira FO, et al. Prognostic factors in locally advanced colon cancer treated by extended resection. *Rev Hosp Clin Fac Med Sao Paulo* 2004;59:361-8.
4. Habr-Gama A, Perez RO, Lynn P. Current issues on the understanding of locally advanced colorectal cancer. *Arq Gastroenterol* 2011;48:223-4.
5. Foxtrot Collaborative Group. Feasibility of preoperative chemotherapy for locally advanced, operable colon cancer: the pilot phase of a randomised controlled trial. *Lancet Oncol* 2012; 13:1152-60.
6. Krishnamurty DM, Hawkins AT, Wells KO, Mutch MG, Silviera ML, Glasgow SC, et al. Neoadjuvant radiation therapy in locally advanced colon cancer: a cohort analysis. *J Gastrointest Surg* 2018;22:906-12.
7. Croner RS, Merkel S, Papadopoulos T, Schellerer V, Hohenberger W, Goehl J. Multivisceral resection for colon carcinoma. *Dis Colon Rectum* 2009;52:1381-6.
8. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene F, Trotti A. *AJCC Cancer Staging Manual*, 7th edition. 2010; Springer, New York, NY: 143-64

9. Wegner RE, Abel S, Monga D, Raj M, Finley G, Nosik S, et al. Utilization of adjuvant radiotherapy for resected colon cancer and its effect on outcome. *Ann Surg Oncol* 2020;27: 825-32.
10. Sauer R, Becker H, Hohenberger W, Rödel C, Wittekind C, Fietkau R, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med* 2004;351:1731-40.
11. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Kryj M. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. *Br J Surg* 2006;93:1215-23.
12. NCCN Guideline. Rectal cancer Version 1 2018. https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf. Accessed 8 May 2018.
13. Hashiguchi Y, Muro K, Saito Y, Ito Y, Ajioka Y, Hamaguchi T, et al. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2019 for the treatment of colorectal cancer. *Int J Clin Oncol* 2020;25:1-42.
14. Cukier M, Smith AJ, Milot L, Chu W, Chung H, Fenech D, et al. Neoadjuvant chemoradiotherapy and multivisceral resection for primary locally advanced adherent colon cancer: a single institution experience. *Eur J Surg Oncol* 2012;38: 677-82.
15. Qiu B, Ding PR, Cai L, Xiao WW, Zeng ZF, Chen G, et al. Outcomes of preoperative chemoradiotherapy followed by surgery in patients with unresectable locally advanced sigmoid colon cancer. *Chin J Cancer* 2016;35:65.
16. Huang CM, Huang MY, Ma CJ, Yeh Y, Tsai HL, Huang CW, et al. Neoadjuvant FOLFOX chemotherapy combined with radiotherapy followed by radical resection in patients with locally advanced colon cancer. *Radiat Oncol* 2017;12:48.
17. Hawkins AT, Ford MM, Geiger TM, Hopkins MB, Kachnic LA, Muldoon RL, et al. Neoadjuvant radiation for clinical T4 colon cancer: a potential improvement to overall survival. *Surgery* 2019;165:469-75.
18. Ngan SY, Burmeister B, Fisher RJ, Solomon M, Goldstein D, Joseph D, et al. Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with T3 rectal cancer: Trans-Tasman Radiation Oncology Group Trial 01.04. *J Clin Oncol* 2012;30:3827-33.
19. Landmann RG, Weiser MR. Surgical management of locally advanced and locally recurrent colon cancer. *Clin Colon Rectal Surg* 2005;18:182-9.
20. Lehnert T, Methner M, Pollok A, Schaible A, Hinz U, Herfarth C. Multivisceral resection for locally advanced primary colon and rectal cancer: an analysis of prognostic factors in 201 patients. *Ann Surg* 2002;235:217-25.
21. Nishikawa T, Ishihara S, Emoto S, Kaneko M, Murono K, Sasaki K, et al. Multivisceral resections for locally advanced colorectal cancer after preoperative treatment. *Mol Clin Oncol* 2018;8:493-8.
22. Kuan FC, Lai CH, Ku HY, Wu CF, Hsieh MC, Liu TW, et al. The survival impact of delayed surgery and adjuvant chemotherapy on stage II/III rectal cancer with pathological complete response after neoadjuvant chemoradiation. *Int J Cancer*. 2017;140:1662-9.
23. Al-Sukhni E, Attwood K, Mattson DM, Gabriel E, Nurkin SJ. Predictors of pathologic complete response following neoadjuvant chemoradiotherapy for rectal cancer. *Ann Surg Oncol* 2016;23:1177-86.
24. Kalady MF, de Campos-Lobato LF, Stocchi L, Geisler DP, Dietz D, Lavery IC, et al. Predictive factors of pathologic complete response after neoadjuvant chemoradiation for rectal cancer. *Ann Surg* 2009;250:582-9.
25. Maas M, Nelemans PJ, Valentini V, Das P, Rödel C, Kuo LJ, 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* 2010;11: 835-44.
26. Han YD, Kim WR, Park SW, Cho MS, Hur H, Min BS, et al. Predictors of pathologic complete response in rectal cancer patients undergoing total mesorectal excision after preoperative chemoradiation. *Medicine (Baltimore)* 2015;94:e1971.
27. Martin ST, Heneghan HM, Winter DC. Systematic review and meta-analysis of outcomes following pathological complete response to neoadjuvant chemoradiotherapy for rectal cancer. *Br J Surg* 2012;99:918-28.
28. Rödel C, Liersch T, Becker H, Fietkau R, Hohenberger W, Hothorn T, et al. Preoperative chemoradiotherapy and postoperative chemotherapy with fluorouracil and oxaliplatin versus fluorouracil alone in locally advanced rectal cancer: initial results of the German CAO/ARO/AIO-04 randomised phase 3 trial. *Lancet Oncol* 2012;13:679-87.
29. Rödel C, Graeven U, Fietkau R, Hohenberger W, Hothorn T, Arnold D, et al. Oxaliplatin added to fluorouracil-based preoperative chemoradiotherapy and postoperative chemotherapy of locally advanced rectal cancer (the German CAO/ARO/AIO-04 study): final results of the multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol* 2015;16:979-89.
30. Gerard JP, Azria D, Gourgou-Bourgade S, Martel-Laffay I, Hennequin C, Etienne PL, et al. Comparison of two neoadjuvant chemoradiotherapy regimens for locally advanced rectal cancer: results of the phase III trial ACCORD 12/0405-Prodige 2. *J Clin Oncol* 2010;28:1638-44.
31. Aschele C, Cionini L, Lonardi S, Pinto C, Cordio S, Rosati G, et al. Primary tumor response to preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer: pathologic results of the STAR-01 randomized phase III trial. *J Clin Oncol* 2011;29:2773-80.
32. O'Connell MJ, Colangelo LH, Beart RW, Petrelli NJ, Allegra CJ, Sharif S, et al. Capecitabine and oxaliplatin in the preoperative multimodality treatment of rectal cancer: surgical end points from National Surgical Adjuvant Breast and Bowel Project trial R-04. *J Clin Oncol* 2014;32:1927-34.
33. Jiao D, Zhang R, Gong Z, Liu F, Chen Y, Yu Q, et al. Fluo-

rouracil-based preoperative chemoradiotherapy with or without oxaliplatin for stage II/III rectal cancer: a 3-year follow-up study. *Chin J Cancer Res* 2015;27:588-96.

34. Deng Y, Chi P, Lan P, Wang L, Chen W, Cui L, et al. Modified FOLFOX6 with or without radiation versus fluorouracil and leucovorin with radiation in neoadjuvant treatment of locally advanced rectal cancer: initial results of the Chinese FOWARC Multicenter, Open-Label, Randomized Three-Arm Phase III Trial. *J Clin Oncol* 2016;34:3300-7.
35. Yamashita K, Matsuda T, Hasegawa H, Mukohyama J, Arimoto A, Tanaka T, et al. Recent advances of neoadjuvant chemoradiotherapy in rectal cancer: future treatment perspectives. *Ann Gastroenterol Surg* 2019;3:24-33.

原　著

局部侵犯型大腸癌病患接受短程放射線治療或同步化學放射治療併廣泛性大腸癌切除成果分析

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背景　局部侵犯型大腸癌通常定義為很大的腫瘤體積，腫瘤侵犯或是沾黏到鄰近的組織或器官。一般來說，局部侵犯型大腸癌常常是無法將腫瘤切除乾淨的疾病。目前來說，直腸癌病患接受前輔助性短程放射線治療或同步化學放射治療已經成為標準的癌症治療步驟選項。但是，局部侵犯型大腸癌病患接受前輔助性短程放射線治療或同步化學放射治療的腳色定位至今仍然不清楚。本篇研究的目的在分析大腸癌病患接受前輔助性短程放射線治療或同步化學放射治療的成果分析。

方法　我們回溯性分析本院於 2008 年 1 月到 2018 年 12 月期間，診斷為局部侵犯型大腸癌及前輔助性短程放射線治療或同步化學放射治療的病患。病患的基本資料，放射線治療毒性，手術成果，病理報告結果，5 年整體存活率和 5 年無疾病存活率資料都被收集起來加以分析結果。

結果　本研究總共收錄 19 位病人。所有病人 T 分期為 T4a 期或 T4b 期，沒有 T3 期。14 位病人 (73.7%) 為臨床 N2 淋巴結陽性。接受短程放射線的病人沒有發生放射治療毒性。接受同步化學放射治療病患則 100% 發生 1 至 2 級的腸胃道毒性副作用。需要多重臟器切除佔 7 位病人 (35.8%)，組織邊緣切除陰性結果佔 78.9%，病理完全反應者僅佔 5.3%，局部復發機率為 5.3%。第 3 期病患平均 5 年整體存活率和 5 年無疾病存活率分別為 91.7% 和 83.3%。

結論　我們的研究指出局部侵犯型大腸癌病患接受前輔助性短程放射線治療或同步化學放射治療併廣泛性大腸癌切除是可行且安全的。

關鍵詞　局部侵犯型大腸癌、大腸癌、短程放射線治療、同步化學放射治療、手術。