Original Article

Short-course Radiation Therapy Followed by Chemotherapy as Preoperative Treatment for Rectal Cancer

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Key Words
Neoadjuvant treatment;
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Background. Currently, neoadjuvant treatment followed by total mesorectal excision is the standard management for locally advanced rectal cancer. There are varied regimens regarding the combination of neoadjuvant radiotherapy and chemotherapy. In this study, we aimed to report the feasibility and early oncological outcomes of preoperative short-course radiation therapy (SRT) followed by consolidative chemotherapy and delayed surgery in patients with rectal cancer.
Materials and Methods. A retrospective review of 39 patients with rectal cancer who underwent neoadjuvant SRT followed by chemotherapy between March 2014 and June 2019 was performed. The regimen of chemotherapy included either mFOLFOX6 or capecitabine and oxaliplatin or oral form 5-fluorouracail alone. Full course chemotherapy was defined as 8 weeks of preoperative chemotherapy after SRT.
Results. All the 39 patients included in this study completed SRT, and 32 patients (82.1%) completed full course of neoadjuvant chemotherapy. One of the 32 patients required dose reduction due to general weakness. Six of the seven patients not completing full course of chemotherapy underwent early surgical intervention, and the remaining one patient achieved clinical completed response (cCR) without subsequent surgery. Of all patients, 4 patient (10.3%) achieved cCR and opted to watch-and-wait policy. Thirty-four patients underwent surgery and 3 (8.8%) of them presented with pathological complete response (pCR). No major treatment-related toxicity or para-operative morbidity and mortality presented.
Conclusion. SRT followed by neoadjuvant chemotherapy is feasible and well tolerated by patients without significant toxicity. It is a safe regimen for patients with rectal cancer and results in acceptable short-term oncological outcomes.
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Surgical management of primary locally advanced rectal cancer is associated with high local and distant recurrence that necessitates multimodality treatment. Currently, neoadjuvant treatment followed by total mesorectal excision is the standard management for locally advanced rectal cancer. There are two widely accepted methods for neoadjuvant radiotherapy, one being the conventional concurrent chemoradiotherapy (CRT) (long-course radiotherapy, 50.4 Gy in 28 daily fractions with 5-fluorouracil [5FU] based concurrent chemotherapy), and the other is the short-course radiotherapy (SRT) (25 Gy in five consecutive daily

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fractions followed by immediate surgery). Two randomized trials, the Trans-Tasman Radiation Oncology Group (TROG) trial and Polish trial, demonstrated no significant difference in overall survival (OS), disease-free survival (DFS), local control, sphincter preservation rate, and Grade 3-4 late toxicities between CRT and SRT. Furthermore, the trials reported lesser acute toxicities after SRT.[1,2]

However, the limited interval between SRT and immediate surgery (within 1 week) without preoperative chemotherapy may result in increased treatment-related complications as well as less tumor downstaging, improved resectability, and sphincter preservation (in low rectal tumors). The Stockholm III trial reported that SRT with delayed surgery (after 4-8 weeks) resulted in significantly lower rates of postoperative complications when compared to immediate surgery (within 1 week) (38% vs. 50%), without statistically compromising the oncological outcomes.[3] This finding was also confirmed in a recent meta-analysis of 1244 patients, which revealed that the delayed surgery group had better pathological outcomes (higher pathologic complete response [pCR] rate) and fewer post-operative complications.[4]

Some studies reported addition of preoperative chemotherapy during the interval between SRT and surgery, and demonstrated lower incidence of complications.[5-8]

There are different regimens on the combination of neoadjuvant radiotherapy and chemotherapy for rectal cancer. In this study, we aimed to report the feasibility and early oncological outcomes of preoperative SRT followed by consolidative chemotherapy and delayed surgery in patients with rectal cancer.

Materials and Methods

Study design and participants

Patients with histologically proven rectal adenocarcinoma who underwent neoadjuvant SRT followed by chemotherapy between March 2014 and June 2019 were reviewed in this study. The internal review board at Chang Gung Memorial Hospital (IRB No.2020 00644B0) approved this retrospective study.

Pretreatment assessment

The pretreatment local staging was performed by physical examination (including digital rectal examination), colonoscopy, and pelvic imaging study (computed tomography, magnetic resonance imaging, or rectal endoscopic ultrasonography). Other mandatory diagnostic investigations comprised contrast-enhanced thorax and abdominopelvic computed tomography scan, complete blood count, liver and renal function tests, as well as serum levels of carcinoembryonic antigen.

Inclusion and exclusion criteria

Patients fulfilling the following criteria were enrolled in this study: T2-T4 or positive regional lymph node (N+) rectal adenocarcinoma located up to 15 cm from the anal verge, and grade 0-2 on the Eastern Cooperative Oncology Group performance status. Patients with one of the following conditions were excluded from this study: incomplete chemotherapy (less than 4 weeks), recurrent tumors after previous surgery, or insufficient data due to poor compliance.

Radiotherapy and chemotherapy protocol

All the patients underwent SRT in five fractions of 5 Gy to a total dose of 25 Gy over 5 consecutive days. The patients were treated by three-dimensional conformal radiotherapy or volumetric modulated arc therapy with 6 or 10 MV photon X-rays. The clinical target volume included the tumor, involved regional lymph nodes, elective pelvic lymph nodes, and the entire mesorectum with adequate margins.

The regimen of consolidative chemotherapy included either modified infusional and bolus 5FU and oxaliplatin (mFOLFOX6), uracil/ftorafur/leucovorin combined with oxaliplatin (Tegafox), infusional 5FU combined with leucovorin or oral form of 5FU alone after completion of radiotherapy. Full course chemotherapy was defined as 8 weeks of preoperative consolidative chemotherapy after SRT. The postoperative

chemotherapy was at the discretion of the attending physician.

Surgical procedure

All participants underwent pre-surgical evaluations after completion of radiotherapy and during chemotherapy. The surgical procedures included local excision, low anterior resection (LAR), Hartmann's operation, and abdominal-perineal resection (APR) at the discretion of the surgeons. The patients were monitored for perioperative complications for 1 month following the surgery (inpatient or outpatient care).

Response assessment

The clinical response to neoadjuvant treatment was assessed by digital rectal examination, colonoscopy, and pelvic imaging study. The pathological response to neoadjuvant treatment was assessed based on the reports of an experienced pathologist in gastrointestinal malignancies according to the Dworak tumor regression grade (TRG). Tumor depth of invasion (ypT) and number of involved lymph nodes (ypN) as well as T/N downstaging were evaluated.

Toxicity assessment

The patients were monitored for acute (from the beginning of radiotherapy to 1-month post-surgery) and late (after 3 months post-surgery) toxicities based on patient-reported complaints, physical examination, and laboratory studies. Treatment-related toxicities were graded according to the Common Terminology Criteria for Adverse Events version 4.0 and the highest grade was recorded for each patient. The patients were also evaluated for perioperative complications including lung atelectasis, bladder dysfunction, anastomosis leakage, peritonitis, delayed surgical wound healing, and formation of enterocutaneous, rectovesical, or rectovaginal fistulas.

Outcomes and analyses

The primary outcomes were complete clinical and pathological responses (cCR and pCR, respectively) to neoadjuvant short-course radiochemotherapy with delayed surgery. The secondary outcomes were feasibility and complications of the treatment. OS and DFS rates were calculated by the Kaplan-Meier survival analysis method. The standpoint for evaluation of OS was the date of the end of radiotherapy. DFS was calculated in patients in whom surgery was performed and R0 resection was achieved, and was defined as the time from radical surgery to the diagnosis of first recurrence. All statistical analyses were performed using SPSS Version 22.0, and a p value of ≤ 0.05 was considered statistically significant.

Results

Pretreatment characteristics

There were 1548 patients diagnosed with rectal cancer between March 2014 and June 2019; 278 patients underwent long course CRT, and 58 patients underwent SRT followed by chemotherapy. The medical records of 58 patients with rectal adenocarcinoma who underwent neoadjuvant SRT followed by chemotherapy were reviewed. Among the 58 patients, 39 patients were enrolled in this study (Fig. 1) and their characteristics are shown in Table 1. The median age of the patients was 57 years (range, 38 to 85 years).

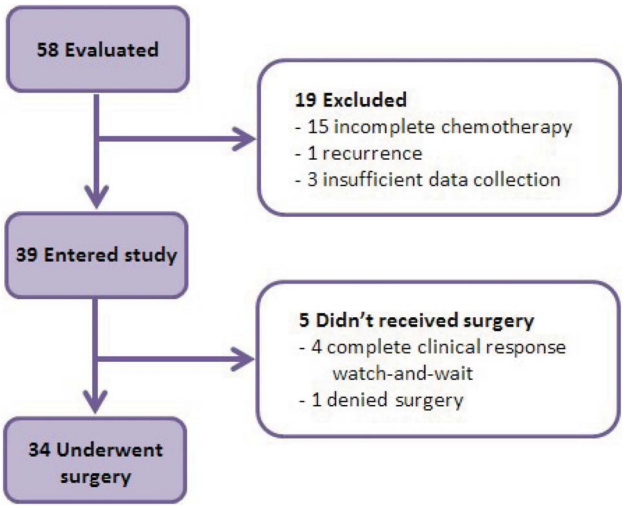

Fig. 1. Flow diagram for patients' inclusion and exclusion.

The median distance of the tumor from the anal verge was 5 cm (range, 2 to 12 cm). The median follow-up time was 16.5 months (range, 1 to 69.2 months).

Treatment tolerance

All the 39 patients completed the course of SRT, 32 (82.1%) patients completed the full course of neoadjuvant chemotherapy, and 32 (82.1%) patients received oxaliplatin-containing neoadjuvant chemotherapy. One of the 32 patients who underwent the full course of neoadjuvant chemotherapy required dose reduction due to general weakness; however, did not present any major toxicity. Six of the seven patients who did not complete the full course of chemotherapy underwent early surgical intervention considering their personal choice, and one patient achieved cCR without subsequent surgery (Table 2).

Thirty-seven (94.9%) patients did not report any toxicity or only grade 1 acute toxicity (including neutropenia, mucositis, nausea, vomiting, diarrhea, peripheral sensory neuropathy, general weakness, allergy, proctitis, and anal pain). Grade 1 acute proctitis was seen in two (5.1%) patients. Grades 2 and 3 acute neutropenia were seen in one patient each (2.6%, respectively). No grade 4 or grade 5 toxicities were recorded (Table 3).

Table 1. Characteristics (all patients, N = 39)

Variables	N	%
Age (median, range)	57 (38-85)	
Sex		
Male	26	66.7
Female	13	33.3
Clinical T stage		
cT1	0	0
cT2	8	20.5
cT3	24	61.5
cT4	7	17.9
Clinical N stage		
cN0	14	35.9
cN1	7	17.9
cN2	18	46.2
Clinical M stage		
cM0	36	92.3
cM1	3	7.7
Pretreatment CEA		
CEA < 5	20	51.3
CEA ≥ 5	19	48.7
ECOG		
0	6	15.4
1	31	79.5
2	2	5.1
DAV		
0~5 cm	24	61.5
5.1~10 cm	14	35.9
10.1~15 cm	1	2.6

CEA, carcinoembryonic antigen; ECOG, Eastern Cooperative Oncology Group, Performance Status; DAV, distance from anal verge.

Table 2. Perioperative therapy (all patients, N = 39)

Variables	N	%
Patients completing short course RT	39	100
Duration of neoadjuvant chemotherapy		
≥ 8 wk	32	82.1
< 8 wk	7	17.9
Neoadjuvant chemotherapy with oxaliplatin		
Yes	32	82.1
No	7	17.9
Patients receiving post-op chemotherapy		
Yes	17	50
No	17	50

Table 3. Treatment related toxicities

Variables	N	%
Chemotherapy related toxicities (all patients, N = 39)		
Hematologic	2	5.1
GI toxicities	9	23.1
Neuropathy	5	12.8
General weakness	3	7.7
Allergy	1	2.6
All nonhematologic	16	41.0
SRT related toxicities (all patients, N = 39)		
Proctitis	2	5.1
Anal pain	2	5.1
Surgery related early toxicities (N = 34)		
Prolonged ileus	1	2.9
Bladder dysfunction	2	5.9
Urethral laceration	1	2.9
Peritonitis	1	2.9
Anastomotic leakage	1	2.9
Surgery related late toxicities (N = 34)		
Bladder dysfunction	1	2.9
Rectovesical fistula	1	2.9
Surgery related morbidity (N = 34)	8	23.5
Surgery related mortality (N = 34)	0	0

GI toxicities: nausea, vomiting, mucositis, diarrhea.

Four (10.3%) patients achieved cCR and opted for the watch-and-wait policy with achievement of organ preservation. These patients had middle to low rectal tumors (4 cm, 5 cm, 6 cm, and 7 cm from the anal verge, respectively), with initial clinical staging of T2N0M0 in three patients and T3N2M0 in one patient. Their follow-up time varied from 7 months to 49 months (7 months, 7 months, 44 months, and 49 months, respectively). However, the pCR rate could not be reported because these patients did not undergo further surgery.

Of the total number of patients, one demonstrated tumor regression after neoadjuvant treatment but refused further surgical intervention. Thirty-four patients underwent surgery and three (8.8%) of them achieved pCR. Among the 34 patients who underwent surgery, 30 (88.2%) patients underwent radical surgery (27 LAR, one Hartmann's operation, and two APR), three underwent local excision, and primary tumor resection could not be achieved in one patient due to inferior vena cava injury with massive bleeding and frozen pelvis noted during the surgery (Table 4). Perioperative stoma was not created in seven (20.6%) patients. Of the 27 patients in whom stoma was created perioperatively, three patients underwent the procedure after radical surgery due to surgery-related complications of peritonitis, anastomosis leakage, and rectovesical fistula, respectively. The median interval from the end of radiotherapy to surgery was 3.2 months (range, 1 to 14.1 months).

Table 4. Operation (OP cases, N = 34)

Variables	N	%
Operation type		
Sphincter-preserving surgery		
LAR	27	79.4
Hartmann	1	2.9
Local excision	3	8.8
APR	2	5.9
No resection	1	2.9
Operation timing		
Elective	34	100
Emergent	0	0
OP intent		
Palliative	2	5.9
Curative	29	85.3
Local excision	3	8.8
Stoma creation		
Yes	24	79.4
No	7	20.6

Eight (23.5%) patients experienced surgery-related morbidities; however, there were no surgery-related mortalities. There were two events (one peritonitis and one anastomosis leakage) of grade 3 early toxicity and one (rectovesical fistula) of grade 3 late toxicity (Table 3).

Treatment response

cCR was reported in four (10.3%) patients. Of the 34 patients who underwent surgery, three (8.8%) achieved pCR (TRG 4), 24 (70.6%) achieved partial pathological response (TRG 3 and TRG 2), and three (8.8%) patients achieved poor pathological response (TRG 1 and TRG 0) (Table 5). Among the three patients who achieved pCR, one had initial clinical staging of T3N0M0 and two had T3N2M0. The patients were followed-up for 4 months, 7 months, and 22 months, respectively, and did not demonstrate local or distant recurrence.

We observed a complete response rate of 17.9% in seven patients, including four patients who achieved cCR and three with pCR. Further subgroup analysis showed no significant difference in the complete response rates between the oxaliplatin and non-oxaliplatin-containing chemotherapy groups (18.8% vs. 14.3%, $p = 0.78$), or between the full and non-full course chemotherapy groups (18.8% vs. 14.3%, $p = 0.78$).

Among the 34 patients who underwent surgery, the sphincter was preserved in 31 (91.2%) patients, and 28 (82.4%) patients achieved R0 resection, of which eight (28.6%) developed distant recurrence but no local recurrence was observed (Table 5). Six patients had non-R0 resection, including two patients with R2 resection and four with R1 resection. Of these, one patient had extremely advanced disease to undergo primary tumor resection, and another underwent the procedure; however, R0 resection could not be achieved due to unresectable liver metastases and positive circumferential resection margin of the primary tumor. Four of the six non-R0 resection patients

Table 5. Pathology reports (OP cases, N = 34)

Variables	N	%
Dworak grade for primary tumor		
0	1	3.3
1	2	6.7
2	7	23.3
3	17	56.7
4	3	10
ypT stage		
ypT0	3	8.8
ypTis	1	2.9
ypT1	3	8.8
ypT2	9	26.5
ypT3	14	41.2
ypT4	4	11.8
ypN stage		
ypN0	27	79.4
ypN1	2	5.9
ypN2	5	14.7
Down-staging		
Yes	22	64.7
No	12	35.3
T down-staging		
Yes	16	47.1
No	18	52.9
N down-staging		
Yes	17	50
No	17	50
Histology type		
Adenocarcinoma	30	88.2
Mucinous	4	11.8
Histology grade		
Well-differentiated	7	21.2
Moderately-differentiated	22	66.7
Poorly-differentiated	4	12.1
Angiolymphatic invasion		
Yes	7	20.6
No	27	79.4
Perineural invasion		
Yes	6	18.2
No	27	81.8
Residual tumor status		
R0	28	82.4
R1 or R2	6	17.6
Resection margin (+)		
Lateral margin (+)	4	11.8
Distal margin (+)	1	2.9

underwent further chemotherapy after the surgery. Chemotherapy was not performed in the other two patients due to old age.

Among the eight patients who developed distant recurrence after R0 resection, seven had ypT3N1-2 disease, and one patient had ypT2N0 disease. The patient with ypT2N0 disease developed solitary lung metastasis 10 months after the surgery, underwent further wedge resection of the lung, and has been disease free for 10 months. Six of the eight patients who developed distant recurrence after R0 resection underwent post-operative chemotherapy. However, two of them did not undergo the procedure due to old age and personal choice.

Treatment outcomes

The 1-year and 2-year OS in the 39 patients were 93% and 87%, respectively (Fig. 2). The 1-year DFS in patients who achieved R0 resection (n = 28) and cCR (n = 4) was 74% (Fig. 3). The 1-year local and distant control rates were 100% and 74%, respectively, among the patients who achieved R0 resection and cCR.

The prolonged interval between SRT and surgery also led to considerable downstaging of the cancer. Among the 34 patients who underwent surgery, 22 (64.7%) patients had tumor downstaging, including T downstaging in 16 (47.1%) patients and N downstaging in 17 (50%) patients (Table 6).

Discussion

Neoadjuvant treatment followed by total mesorectal excision is currently the standard of care in patients with locally advanced rectal cancer. SRT followed by chemotherapy is an accepted alternative to long-course chemoradiation in such patients as a preoperative treatment for tumor downstaging, improving resectability, sphincter preservation, and improving local control.[1,2]

The TROG trial showed that SRT had similar postoperative complications but significantly less acute adverse events compared to long-course chemoradiotherapy.[2,9] However, the major concern of the short-course regimen is the fear of increase in treatment-related complications.[10] Studies have reported negligi-

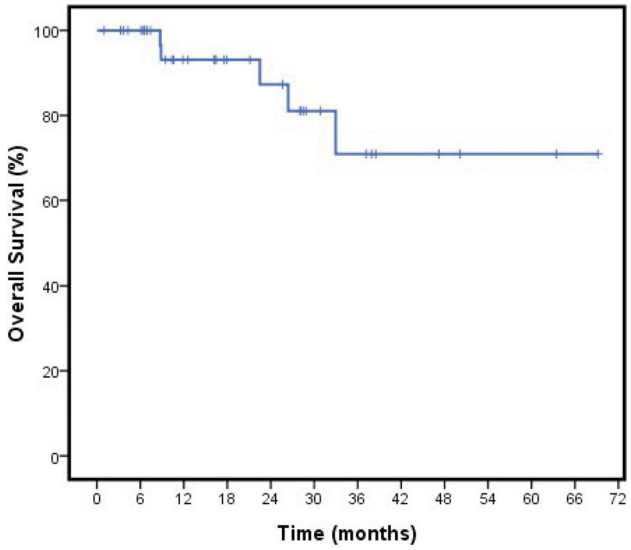

Fig. 2. Overall survival (OS).

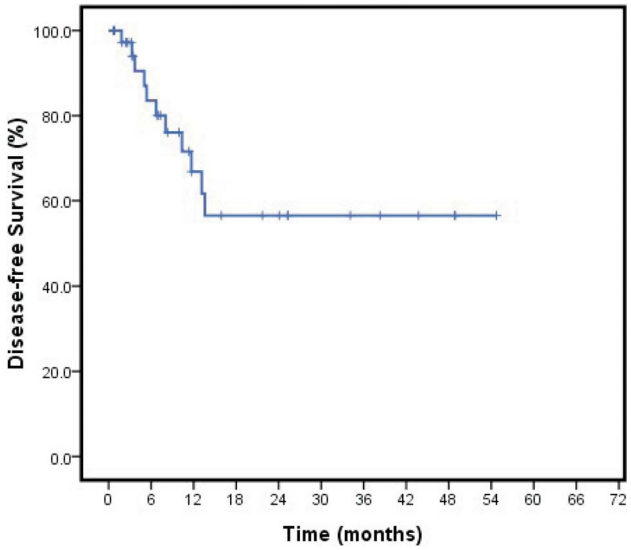

Fig. 3. Disease-free survival (DFS).

bly increased risk of treatment-related complications by lengthening the interval between radiotherapy and surgery, compared to long-course chemoradiotherapy.[11] The concept of delayed surgery after SRT was also tested in the Stockholm III trial, which revealed significantly lower risk of post-operative complications in the SRT with delayed surgery group compared to the immediate surgery group (38% vs. 50%) without compromising the oncological outcomes.[3]

Some studies reported on additional preoperative systemic chemotherapy during the delayed period between radiotherapy and surgery, and testified that SRT and consolidative chemotherapy was a safe and feasible treatment strategy in treatment of rectal cancer. Furthermore, these studies reported additional benefits of selective organ preservation in patients who achieved cCR, and a more convenient and cost-effective way of delivering pelvic RT.[12-17]

In this retrospective study, we demonstrated that preoperative chemotherapy following SRT had an acceptable toxicity profile, similar to that reported in some previous studies. No toxicity or only grade 1 acute toxicity was observed in 37 (94.9%) patients, and no cases of grade 4 or grade 5 toxicities were observed. The Japanese study by Naohito et al. demonstrated the safety and good tumor regression rate of induction SOX (S-1 + oxaliplatin) plus cetuximab therapy and SRT.[5] A Korean study by Chung et al. demonstrated similar toxicities between short- and long-course chemoradiotherapy with infusional 5FU chemotherapy.[7] The KROG 10-01 phase II trial showed high grade 3 or more toxicities (38%) following bolus 5FU chemotherapy and SRT, whereas the KROG 11-02 trial reported more acceptable safety profiles following oral capecitabine and SRT.[6,8]

Table 6. Comparison of pretreatment clinical stage and pathology stage (OP cases, N = 34)

	cT2	cT3	cT4		cN0	cN1	cN2
yPT0		3		yPN0	9	4	13
yPTis		1		yPN1		2	
yPT1		3		yPN2		1	4
yPT2	4	5					
yPT3	1	9	4				
yPT4		1	3				

A systematic review of 16 studies was conducted by Bujko et al. in 2014, including ten studies of SRT alone with delayed surgery (1343 patients) and six studies of SRT with consolidative chemotherapy (244 patients). The study proposed lengthening the interval between radiotherapy and surgery and reported approximately 10% increase in the pCR in the group that underwent SRT alone with delayed surgery. Furthermore, SRT with consolidative chemotherapy yielded a pCR of over 20% (varied between 21% and 26%) and appeared to be a promising treatment for locally advanced rectal cancer.[18] A single arm phase II prospective trial was conducted in Iran in 2018, on a study

population with T3-4 or nodal positive disease, and showed that SRT with consolidative chemotherapy followed by delayed surgery was associated with promising oncological outcomes (pCR rate: 30.8%, eight of 26 patients; 3-year OS: 65%, 3-year local control: 94%).[19]

We presented the safety and efficacy of preoperative SRT and chemotherapy in this study for the treatment of rectal cancer. Another benefit of SRT is that the procedure is associated with lower costs and duration of treatment, which is important in countries with limited health expenditure and may lead to better treatment compliance.

Some ongoing randomized multicenter phase III studies (RAPIDO and STELLAR trials) aim to compare the oncological outcomes of SRT followed by consolidative chemotherapy with conventional concurrent chemoradiotherapy in locally advanced rectal cancer.[20-23] The interim analysis of the STELLAR trial that primarily enrolled 100 patients revealed that the acute toxicities and surgical complications were acceptable and comparable in both groups; however, patients in the SRT and consolidative chemotherapy group showed better treatment compliance.[23]

The main limitations of this study include the small sample size, retrospective design, varied chemotherapy regimens and selection bias. There is also another limitation that some data concerning clinicopathological characteristics were missing from this study, which might influence outcome. Moreover, some of the patients underwent computed tomography rather than magnetic resonance imaging or rectal endoscopic ultrasonography for pelvic staging, which could have led to incorrect clinical staging. In addition, longer follow-up to study the late effects of SRT and the local control rate are warranted. Further randomized trials should be conducted comparing SRT with the conventional long-course chemoradiotherapy.

Conclusion

Short-course radiotherapy followed by neoadjuvant chemotherapy is feasible and well tolerated by patients without significant toxicity. It is a safe regimen for patients with rectal cancer and results in acceptable short-term oncological outcomes.

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原　著

短期療程放射治療接著進行化療作為直腸癌的術前治療

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背景　術前輔助性治療後進行直腸全繫膜切除手術為目前對於局部侵犯性直腸癌之標準治療方式。術前輔助性治療中，放療及化療相互搭配的治療選項眾多，本研究目的是展示短程放療後行化療作為直腸癌術前輔助性治療的可行性及短期治療成果。

方法　挑選本院 2014 年 3 月至 2019 年 6 月診斷直腸癌並接受短程放療及化療作為術前輔助性治療的病人進行回溯性研究。分析術前輔助性治療相關副作用、手術方式及併發症、腫瘤臨床病理分期及治療成果。

結果　39 位納入研究的病人均完整接受短程放療。32 位病人接受完整療程之術前化療。4 位病人在短程放療及化療後達到腫瘤臨床完全緩解 (cCR) 並接受等待觀察療法 (watch and wait)。34 位病人在短程放療及化療後接受手術，其中 3 位病人達到病理完全緩解 (pCR)。未觀察到放化療及手術相關之嚴重併發症。

結論　短程放療後行化療作為直腸癌術前輔助性治療是可行且安全的。

關鍵詞　輔助性治療、短期療程放射治療、鞏固性化學治療、直腸癌。