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Original Article

Short-course radiotherapy with delayed surgery versus conventional chemoradiotherapy: comparison of short-term outcomes in patients with T_{3-4} rectal cancer

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Abstract: Introduction: The aim of this study was to compare short-term outcomes between short-course radiotherapy with delayed surgery (SRT-delay) and a standard conventional chemoradiotherapy (CRT) regimen. Methods: All cases were evaluated based on their clinicopathological features and surgical outcomes. Normality of the distribution was assessed using Kolmogorov-Smirnov test. Students t-test was used to compare means of two independent quantitative data sets. The differences between independent two category data groups were evaluated by Fisher exact test. A two-tailed *P* value less than 0.05 considered to be significant. Results: From January 2014 until December 2017, 98 patients were treated using the SRT-delay regimen and 98 patients were treated using the CRT regimen. The pathological complete response rate (PCR) was 7.14% after RT and 11.22% after CRT. Downstaging to ypT_0, T_1, and T_2 was observed in almost 21.43% of cases in RT group and 25.51% cases in CRT group. In consideration of hospital stay, and medical costs, a significant elevation was observed in the CRT group (all $P>0.05$). No differences between the two groups was observed in the rates of complications (all $P>0.05$). As for toxic and adverse effects, significant elevation was found in grade III to IV in the CRT group ($P<0.05$). Conclusion: The SRT-delay regimen was not inferior in terms of the downstaging effect, and a less toxic and adverse effects on III to IV grade was observed compared with the CRT regimen for T_{3-4} rectal cancer.

Keywords: Short-course radiotherapy, short-term outcomes, T_{3-4} rectal cancer

Introduction

There are expert consensus concerning patients with locally advanced rectal cancer (LACR) (stage II to III), who should undergo neoadjuvant radiotherapy (RT) [1-4]. Nevertheless, the option of neoadjuvant chemotherapy remains controversial [5-7]. In NCCN guidelines on rectal cancer by American specialists [8, 9], preoperative chemoradiotherapy (CRT) is considered as the optimal option for patients harboring LARC. Nevertheless, preoperative short-range RT, long-term concurrent chemoradiation, or long-term RT is recommended in ESMO guidelines [10-12]. Short-range RT is given priority in the majority of European countries. In our clinical experience, diverse clinical features, as well as economic factors should be taken into consideration in patients with LARC in clinical practice.

At present, preoperative short-course RT along with immediate radical surgery (TME), and CRT with TME surgery within 6-8 weeks represent the two major neoadjuvant therapeutic strategies for resectable LARC [11, 13], which are globally applied in daily clinical practice. Based on the outcomes of the Swedish rectal cancer trial [14], the Stockholm II Trial [15] as well as preoperative RT, short-course RT of 25 Gy over 5 consecutive days played an effective role in tumor control of rectal cancer [16]. RT regimen decreased local recurrence, and even enhanced survival in certain trials. Low cost as well as convenience of patients is regarded as the main benefit of the conventional SRT regimen.

Some studies have demonstrated that better local control is obtain from CRT compared to RT alone with the same dose [11, 13], indicating that the drawbacks of the RT regimen are asso-

Table 1. Demographics and clinicopathologic characteristics of patients

Characteristic	RT group (N=98)		CRT group (N=98)		*P*-value
Age (yr) mean ± SD	59.56 ± 13.32 60 (19-75)		58.95 ± 14.46 58 (23-75)		0.853
Tumor size (mm)	48.02 ± 11.90 41 (10-60)		48.63 ± 11.54 40 (15-60)		0.781
Performance status					
0	92	93.88%	92	93.88%	1
1	4	4.08%	4	4.08%	
2	2	2.04%	2	2.04%	
Distance (mm)	45.56 ± 6.32 46 (8-70)		46.12 ± 6.72 41 (7-70)		0.953
Gender					
Female	51	52.04%	41	41.84%	0.152
Male	47	47.96%	57	58.16%	
Primary Site					
Middle third (5-7 cm)	42	42.86%	41	41.84%	
Lower third (0-5 cm)	56	57.14%	57	58.16%	
Grade					
I category	5	5.10%	2	2.04%	0.588
II category	8	8.16%	7	7.14%	
III category	82	83.67%	84	85.71%	
IV category	3	3.06%	5	5.10%	
CT category					
T3	62	63.27%	58	59.18%	
T4a	36	36.73%	40	40.82%	
CN category					
N0	10	10.20%	9	9.18%	
N1	88	89.80%	89	90.82%	

RT: neoadjuvant radiotherapy, CRT: neoadjuvant chemoradiotherapy, Yr: year, cT category: Clinical T stage. cN category: Clinical N stage. *: $P<0.05$: statistically significant meaning.

ciated with failure in down-staging, late morbidity, as well as a lack of verified elevation in sphincter preservation rate [17, 18]. Hence, RT regimens are not generally administered in the United States. In contrast, long-course CRT is the standard therapeutic regimen for rectal cancer. Nevertheless, failure of detection of survival benefit leads to uncertainty concerning the superiority of the two preoperative therapeutic regimens.

To this end, it is of great significance to conduct randomized controlled trials (RCTs) to accurately estimate this specific correlation in China. Herein, the study was designed to exploit the short-term results of the RT-delayed regimen, followed by comparison between it and the standard regimen of CRT in rectal cancer (tumor stage III to IV).

Materials and methods

Recruitment of participants

A prospective randomized study was carried out from January 2014 until December 2017, in a single university center. Each patient provided written informed consent before participating in the study. The trial was approved by the Regional Biomedical Ethics Committees.

The inclusion criteria were as follows: 1) adv-anced rectal cancer; 2) adenocarcinoma confirmed by histopathology; 3) physical fitness suitable for surgery; 4) D2 lymphadenectomy; and 5) no prior history of any type of adjunctive therapy; 6) enteroscopy under the edge of anal margin within 7 cm; 7) tumor size less than 6 cm; 8) ECOG 0-1, ASA I-III; 9) signed written consent.

The exclusion criteria were as follows: 1) younger than 18 years older than 75 years of age; 2) previous or concomitant other cancer; 3) previous or concomitant gastrectomy for benign disease; 4) previous chemotherapy or radiotherapy; 5) esophageal involvement; or 6) distant metastatic disease; 7) patients requiring acute surgical resection with intestinal obstruction, intestinal perforation, and intestinal hemorrhage; 8) previous history of colorectal surgery; 9) combined organ excision; 10) ASA IV or V; 11) pregnant woman.

The clinical staging was done according to the American Joint Committee on Cancer (AJCC) Cancer staging Manual, 6th edition and based on ERUS and/or pelvic CT and/or MRI findings for T and N categories and chest X-ray, abdominal ultrasound and/or CT for M category. Detailed baseline methods of staging, pathological findings and staging (ypT, ypN, CRM, pCR, etc.), as

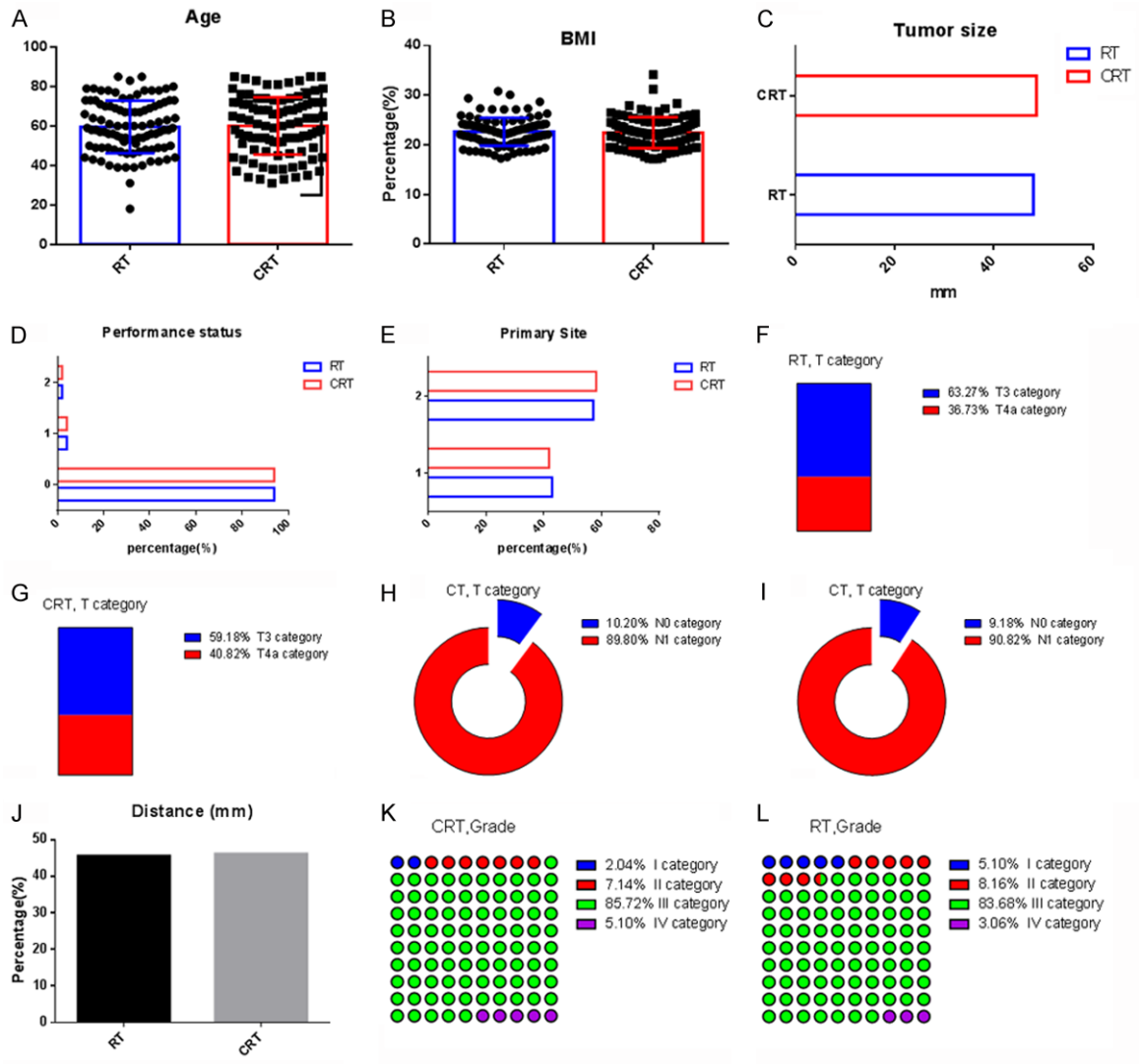

Figure 1. Demographics and clinicopathologic characteristics of patients. A: Two groups of age; B: Two groups of BMI; C: Two groups of tumor size; D: Two groups of PFS; E: Two groups of site; F: RT group of T category; G: CRT group of T category; H: RT group of N category; I: CRT group of N category; J: Two groups of distance; K: CRT group of grade; L: RT group of grade.

well as information regarding surgical management, perioperative complications etc. are presented in the recently published article by Latkauskas et al. [19].

Randomization

A simple randomization method was used with numbered opaque envelopes containing treatment allocations. After screening, patients with stage (II-III) resectable rectal cancer were randomly assigned to one of two treatment arms: short-course preoperative radiotherapy (RT) with delayed surgery, RT 25 Gy/5 fr, 5 Gy per fraction in 5 days following TME surgery after 6-8 weeks, then follow-up; or conventional chemoradiotherapy (CRT) with delayed surgery: RT 50 Gy/25 fr, 2 Gy per fraction over 5 weeks concomitant with fluorouracil (5-FU) and leucovorin (Lv) chemotherapy (5-FU 400 mg/m^2/day i/v 1 h infusion 1-4 days and Lv 20 mg/m^2/day bolus i/v injection 1-4 days) on the 1st and 5th week of RT following TME surgery after 6-8 weeks; then within 8 weeks period adjuvant chemotherapy of 5-FU (400 mg/m^2/day i/v 1 h infusion 1-5 days) and Lv (20 mg/m^2/day bolus i/v injection 1-5 day) was started for 4 cycles every 4 weeks, then follow-up was performed.

Table 2. Surgery performed, pathological characteristics

Characteristic	RT group (N=98)		CRT group (N=98)		*P*-value
YPT category					
T1	9	9.18%	7	7.14%	0.873
T2	55	56.12%	49	50.00%	
T3	29	29.59%	36	36.73%	
T4a	5	5.10%	4	4.08%	
T4b	2	2.04%	2	2.04%	
YPN category					
Negative	62	63.27%	74	75.51%	0.063
Positive	36	36.73%	24	24.49%	
PCR rate (%)	7	7.14%	11	11.22%	0.323
CRM rate (%)	4	4.08%	3	3.06%	0.700
Down staging (%)	21	21.43%	25	25.51%	0.614
Differentiation					
Well	31	31.63%	35	35.71%	0.271
Moderately	62	66.33%	53	54.08%	
Poor	5	5.1%	10	10.20%	
Hospital stay (d)	24.05 ± 2.53 29 (19-44)		87.70 ± 3.08 89 (77-105)		0.000*
Cost (USA dollar)	9941.82 ± 132.46		15122.42 ± 216.75		0.000*

RT: neoadjuvant radiotherapy, CRT: neoadjuvant chemoradiotherapy, yPT: pathological T staging after neoadjuvant therapy. yPN: pathological N staging after neoadjuvant therapy. pCR: pathologic complete response. CRM: circumferential margin. *: $P<0.05$: statistically significant meaning.

Irradiation technique

Patients randomized to short-course RT (5 Gy×5 fr) received a total dose of 25 Gy over 5 consecutive days, from Monday to Friday. For patients, randomized to long-course RT, daily fractional dose was 2 Gy in 25 fractions over 5 weeks (total dose 50 Gy). RT technique arrangement was identical in the two treatment groups. The target volume included the primary tumor, adjacent lymph nodes and presacral region. The target volume extended from the top of the sacrum to 5 cm below the primary tumor. Laterally, it included pelvic sidewalls and internal iliac nodes. Posteriorly, the presacral lymph nodes and sacral hollow were covered. Anteriorly, an adequate margin was left to cover the tumor (including the posterior vaginal wall in women).

Follow-up

After treatment, follow-up visits were performed every 3 months for the first 2 years; later, every 6-12 months for at least 5 years. Evaluation consisted of physical examination, abdominal ultrasound, chest X-ray, and colonoscopy. CT and/or MRI were performed if there was suspicion of local or distant recurrence.

Statistical analysis

The trial was designed to test the non-inferiority of short-term curative effect in the RT versus CRT group. Assuming equal trial groups, non-inferiority margin of hazard ratio of 0.8, 50% of event rate, 5% type I error, and 80% power, the sample size was estimated at least 150 subjects. Assuming the probability of dropouts in a range of 5-10%, enrollment of at least 150 patients was required.

Descriptive statistics were used to describe demographic patients' characteristics. The normality of the distribution was assessed using Kolmogorov-Smirnov test. The Student t-test was used to compare means of two independent quantitative data sets. The differences between independent two category data groups were evaluated by the Fisher exact test. A two-tailed *P* value less than 0.05 considered to be significant. Statistical analysis was performed using Statistical Product for Social Sciences (SPSS) 19.0 software (SPSS, Inc, Chicago, IL, USA).

Results

Clinicopathological characteristics

Patients (N=200) who met the inclusion criteria were randomized to RT or CRT schedules, 98 patients in each arm. Four patients (4%) were ineligible (withdrawal, due to metastases found during the operation (2 in CRT group). Protocol violations were identified in 2 (2%) patients in the RT arm-they had no surgery (1 refused, 1 due to cardiac event), and also were not analyzed. All eligible patients were included in statistical analysis.

From January 2014 to December 2017, 196 patients were enrolled into the study. Patient characteristics (N=196) in two groups at randomization were similar and well balanced

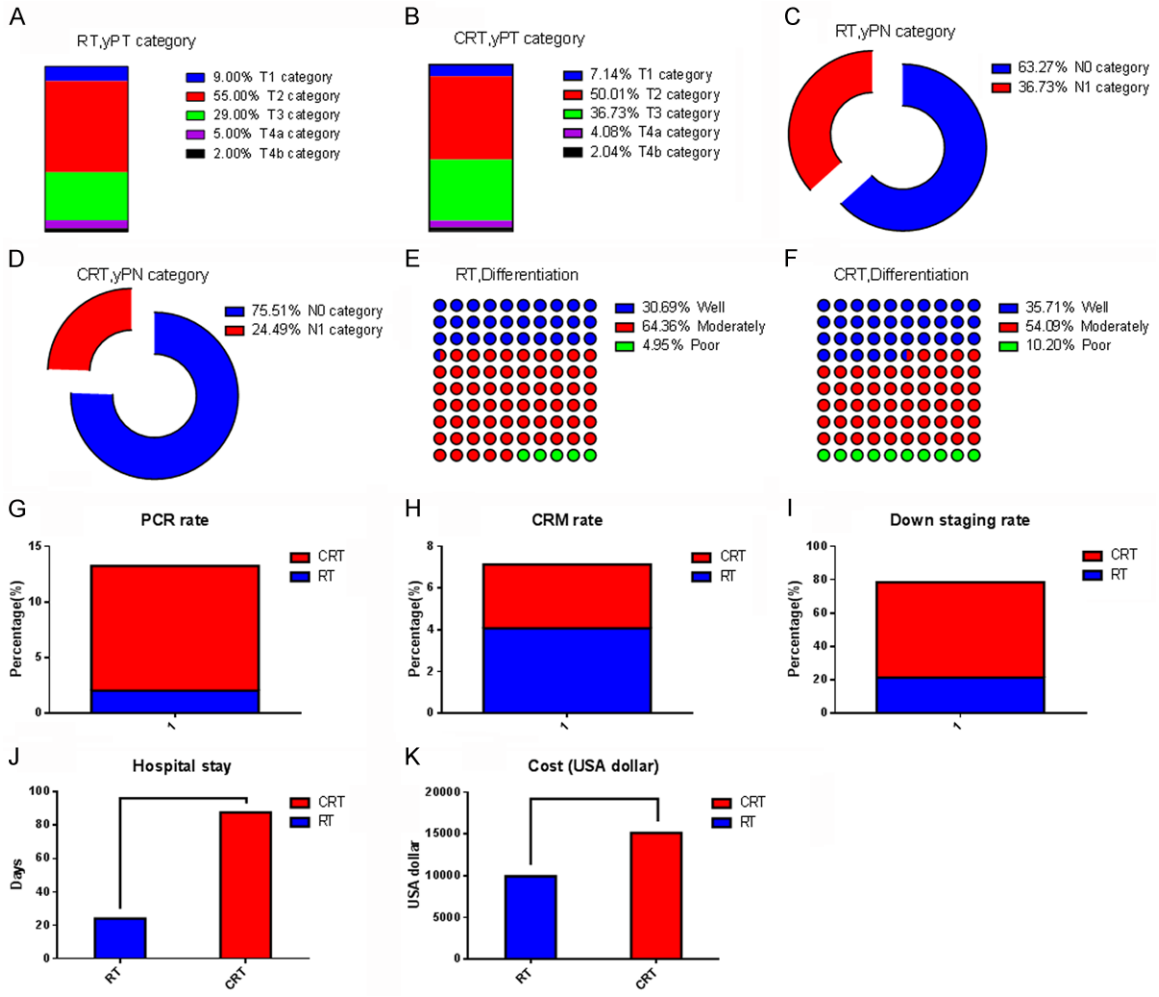

Figure 2. Surgery performed and pathological characteristics. A: RT group of ypT category; B: CRT group of ypT category; C: RT group of ypN category; D: CRT group of ypN category; E: RT group of Differentiation; F: CRT group of Differentiation; G: Two groups of PCR rate; H: Two groups of CRM rate; I: Two groups of down staging rate; J: Two groups of hospital stay; K: Two groups of cost.

(**Table 1** and **Figure 1**). The pathological complete response rate (PCR) was 7.14% after RT and 11.22% after CRT. Downstaging to ypT_0, T_1 and T_2 was observed in almost 21.43% of cases in RT group and 25.51% cases in CRT group. Furthermore, downstaging to ypN_0, and N_1 was observed in almost 63.27% of cases in RT group and 77.51% in CRT group. As for CRM rate, there is 4.08% in RT group and 3.06% in CRT group, but there were no significant differences between the groups. In consideration of hospital stay, and medical costs, we can see an elevated significantly in the CRT group (all *P*>0.05, **Table 2** and **Figure 2**).

Table 3 and **Figure 3** shows postoperative complications. There were no differences between the 2 groups in the rates of anastomotic leakage (1.02% for RT group versus 3.06% for CRT group), intra-abdominal infection (3.06% for RT group versus 3.06% for CRT group), wound infection (1.02% for RT group versus 1.02% for CRT group), or ileus (3.06% for RT group versus 2.04% for CRT group) (all P>0.05).

Table 4 and **Figure 4** shows toxic and adverse effects. There were no differences between the 2 groups in I-II grade (Grade I: 9.18% of RT group versus 7.14% of CRT group; Grade II: 7.14% of RT group versus 8.16% of CRT group). However, a significant elevation was found in the III-IV grade (Grade III: 5.10% of RT group versus 17.35% of CRT group; Grade IV: 0% of RT group versus 9.18% of CRT group, all *P*<0.05).

Table 3. Postoperative complications

Complication	RT group (N=98)		CRT group (N=98)		*P*-value
Anastomotic leakage	1	1.02%	3	3.06%	0.766
Intraabdominal infection	3	3.06%	3	3.06%	
Wound infection	1	1.02%	1	1.02%	
Ileus	3	3.06%	2	2.04%	

RT: neoadjuvant radiotherapy, CRT: neoadjuvant chemoradiotherapy. *: *P*<0.05: statistically significant meaning.

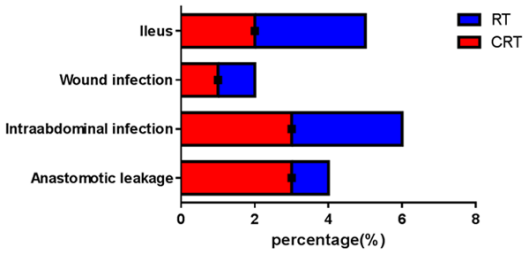

Figure 3. Postoperative complications.

Table 4. Toxic and adverse effects

	RT group (N=98)		CRT group (N=98)		*P*-value
I	9	9.18%	7	7.14%	0.015
II	7	7.15%	8	8.16%	
III	5	5.10%	17	17.35%	
IV	0	0.00%	9	9.18%	

RT: neoadjuvant radiotherapy, CRT: neoadjuvant chemoradiotherapy. *: *P*<0.05: statistically significant meaning.

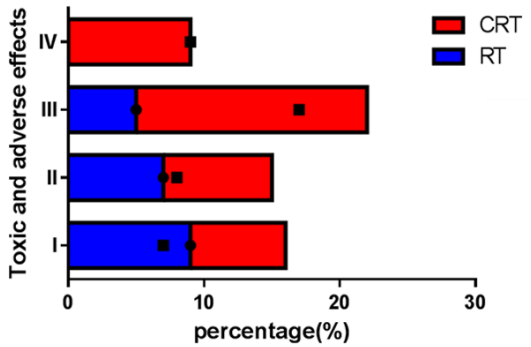

Figure 4. Toxic and adverse effects.

Discussion

To our knowledge, this study is among the recent studies of systematical evaluation of the clinical significance in a subgroup of patients with LARC (stage$_{II-III}$), who underwent neoadjuvant RT or neoadjuvant CRT in China. As a result, the short-term curative effects were not significantly different, including the down-staging, CRM as well as PCR rates. The findings are consistent with Naohito et al. [3], who demonstrated that RT-delay regimen was non-inferior to CRT regimen in consideration of PCR and CRM outcomes as well as down-staging effect in middle and low rectal cancer (tumor stage$_{II-III}$).

In consideration of medical costs, the RT-delay regimen costs approximately $9,941.82, while the cost of CRT regimen is up to approximately $15,122.42. Moreover, in terms of convenience of patient, the waiting period for RT-delay regimen is approximately 24 days, while the waiting period after CRT is approximately one month, which is more than three months since the beginning of RT. Taken together, the relatively low cost and convenience of patients represent the two main benefit for RT-delay regimen, which is supported by the outcomes from Japanese scholars Folkesson et al. [4].

Postoperative complications were statistically significant between two regimens, including the rates of wound infection (1.02% in RT group versus 1.02% in CRT group), anastomotic leakage (1.02% in RT group versus 3.06% in CRT group), ileus (3.06% in RT group versus 2.04% in CRT group) and intra-abdominal infection (3.06% in RT group versus 3.06% in CRT group) (all *P*>0.05).

A Germany study [20] revealed that the preoperative toxic death rate was 1% in the preoperative RT arm, which was 2% in the R03 trial carried out by the National Surgical Adjuvant Breast and Bowel Project (NSABP) [21]. Here, there was no mortality case in either group. In our experience, subjects undergoing CRT regimen exhibited a stronger degree of toxicity as well as adverse effects. However, in this study, the toxicity as well as adverse effects of grade I to II were not significantly different between two regimens, in spite of a significant elevation of adverse effects of grade III to IV (5.10% vs 18.94%, *P*=0.015).

There are limitations in the present study. First, this study was initially designed as a single-center RCT, nevertheless, 196 patients were finally enrolled in the study, which was likely to contribute to clinical bias. Additionally, the use

of telephone for follow-up might result in recall bias.

Collectively, the findings demonstrate that preoperative short-course RT along with immediate TME was not inferior in terms of the downstaging effect in patients harboring LARC, which also resulted in less toxicity as well as fewer adverse effects, accompanied by a shortened hospitalization, and decreased medical cost.

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Disclosure of conflict of interest

None.

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References

[1] Dimitriou N, Michail O, Moris D and Griniatsos J. Low rectal cancer: sphincter preserving techniques-selection of patients, techniques and outcomes. World J Gastrointest Oncol 2015; 7: 55-70.

[2] Lee CM, Cho JM, Jang YJ, Park SS, Park SH, Kim SJ, Mok YJ, Kim CS and Kim JH. Should lymph node micrometastasis be considered in node staging for gastric cancer?: the significance of lymph node micrometastasis in gastric cancer. Ann Surg Oncol 2015; 22: 765-771.

[3] Beppu N, Matsubara N, Noda M, Yamano T, Kakuno A, Doi H, Kamikonya N, Kimura F, Yamanaka N, Yanagi H and Tomita N. Short-course radiotherapy with delayed surgery versus conventional chemoradiotherapy: a comparison of the short- and long-term outcomes in patients with t3 rectal cancer. Surgery 2015; 158: 225-235.

[4] Folkesson J, Birgisson H, Pahlman L, Cedermark B, Glimelius B and Gunnarsson U. Swedish rectal cancer trial: long lasting benefits from radiotherapy on survival and local recurrence rate. J Clin Oncol 2005; 23: 5644-5650.

[5] Pavlidis TE, Pavlidis ET and Sakantamis AK. The role of intersphincteric resection in very low rectal cancer. Ann Surg Oncol 2017; 24: 612-613.

[6] Takase S, Kamigaki T, Yamashita K, Nakamura T, Nishimura H and Sasaki R. [Preoperative chemoradiotherapy for resectable lower rectal cancer]. Gan To Kagaku Ryoho 2009; 36: 2006-2008.

[7] Huber FT, Stepan R, Zimmermann F, Fink U, Molls M and Siewert JR. Locally advanced rectal cancer: resection and intraoperative radiotherapy using the flab method combined with preoperative or postoperative radiochemotherapy. Dis Colon Rectum 1996; 39: 774-779.

[8] Benson AB 3rd, Venook AP, Bekaii-Saab T, Chan E, Chen YJ, Cooper HS, Engstrom PF, Enzinger PC, Fenton MJ, Fuchs CS, Grem JL, Grothey A, Hochster HS, Hunt S, Kamel A, Kirilcuk N, Leong LA, Lin E, Messersmith WA, Mulcahy MF, Murphy JD, Nurkin S, Rohren E, Ryan DP, Saltz L, Sharma S, Shibata D, Skibber JM, Sofocleous CT, Stoffel EM, Stotsky-Himelfarb E, Willett CG, Gregory KM and Freedman-Cass D. Rectal cancer, version 2.2015. J Natl Compr Canc Netw 2015; 13: 719-728; quiz 728.

[9] Reyngold M, Niland J, ter Veer A, Milne D, Bekaii-Saab T, Cohen SJ, Lai L, Schrag D, Skibber JM, Small W Jr, Weiser M, Wilkinson N and Goodman KA. Neoadjuvant radiotherapy use in locally advanced rectal cancer at nccn member institutions. J Natl Compr Canc Netw 2014; 12: 235-243.

[10] Chen G and Wang Y. [Updates of 2017 esmo guideline for rectal cancer]. Zhonghua Wei Chang Wai Ke Za Zhi 2017; 20: 1236-1242.

[11] Glimelius B, Tiret E, Cervantes A, Arnold D; ESMO Guidelines Working Group. Rectal cancer: esmo clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013; 24 Suppl 6: vi81-88.

[12] Schmoll HJ, Van Cutsem E, Stein A, Valentini V, Glimelius B, Haustermans K, Nordlinger B, van de Velde CJ, Balmana J, Regula J, Nagtegaal ID, Beets-Tan RG, Arnold D, Ciardiello F, Hoff P, Kerr D, Kohne CH, Labianca R, Price T, Scheithauer W, Sobrero A, Tabernero J, Aderka D, Barroso S, Bodoky G, Douillard JY, El Ghazaly H, Gallardo J, Garin A, Glynne-Jones R, Jordan K, Meshcheryakov A, Papamichail D, Pfeiffer P, Souglakos I, Turhal S and Cervantes A. Esmo consensus guidelines for management of patients with colon and rectal cancer. a per-

sonalized approach to clinical decision making. Ann Oncol 2012; 23: 2479-2516.
[13] Valentini V, Aristei C, Glimelius B, Minsky BD, Beets-Tan R, Borras JM, Haustermans K, Maingon P, Overgaard J, Pahlman L, Quirke P, Schmoll HJ, Sebag-Montefiore D, Taylor I, Van Cutsem E, Van de Velde C, Cellini N, Latini P and Scientific C. Multidisciplinary rectal cancer management: 2nd european rectal cancer consensus conference (eureca-cc2). Radiother Oncol 2009; 92: 148-163.
[14] Swedish Rectal Cancer T, Cedermark B, Dahlberg M, Glimelius B, Pahlman L, Rutqvist LE and Wilking N. Improved survival with preoperative radiotherapy in resectable rectal cancer. N Engl J Med 1997; 336: 980-987.
[15] Cedermark B, Johansson H, Rutqvist LE and Wilking N. The stockholm i trial of preoperative short term radiotherapy in operable rectal carcinoma. A prospective randomized trial. Stockholm colorectal cancer study group. Cancer 1995; 75: 2269-2275.
[16] van Gijn W, Marijnen CA, Nagtegaal ID, Kranenbarg EM, Putter H, Wiggers T, Rutten HJ, Påhlman L, Glimelius B, van de Velde CJ; Dutch Colorectal Cancer Group. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled tme trial. Lancet Oncol 2011; 12: 575-582.
[17] Birgisson H, Påhlman L, Gunnarsson U, Glimelius B; Swedish Rectal Cancer Trial Group. Adverse effects of preoperative radiation therapy for rectal cancer: long-term follow-up of the swedish rectal cancer trial. J Clin Oncol 2005; 23: 8697-8705.
[18] Marijnen CA, van de Velde CJ, Putter H, van den Brink M, Maas CP, Martijn H, Rutten HJ, Wiggers T, Kranenbarg EK, Leer JW and Stiggelbout AM. Impact of short-term preoperative radiotherapy on health-related quality of life and sexual functioning in primary rectal cancer: report of a multicenter randomized trial. J Clin Oncol 2005; 23: 1847-1858.
[19] Latkauskas T, Pauzas H, Kairevice L, Petrauskas A, Saladzinskas Z, Janciauskiene R, Gudaityte J, Lizdenis P, Svagzdys S, Tamelis A and Pavalkis D. Preoperative conventional chemoradiotherapy versus short-course radiotherapy with delayed surgery for rectal cancer: results of a randomized controlled trial. BMC Cancer 2016; 16: 927.
[20] Sauer R, Fietkau R, Wittekind C, Martus P, Rodel C, Hohenberger W, Jatzko G, Sabitzer H, Karstens JH, Becker H, Hess C and Raab R. Adjuvant versus neoadjuvant radiochemotherapy for locally advanced rectal cancer. A progress report of a phase-iii randomized trial (protocol cao/aro/aio-94). Strahlenther Onkol 2001; 177: 173-181.
[21] Hyams DM, Mamounas EP, Petrelli N, Rockette H, Jones J, Wieand HS, Deutsch M, Wickerham L, Fisher B and Wolmark N. A clinical trial to evaluate the worth of preoperative multimodality therapy in patients with operable carcinoma of the rectum: a progress report of national surgical breast and bowel project protocol r-03. Dis Colon Rectum 1997; 40: 131-139.