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Benefits of Adjuvant Chemotherapy for Clinical T3-4N0 Rectal Cancer After Preoperative Chemoradiotherapy

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While the guidelines for adjuvant chemotherapy (AC) for colon cancer are relatively standardized, those for early rectal cancer are still lacking. We therefore evaluated the role of AC in clinical stage II rectal cancer treatment after preoperative chemoradiotherapy (CRT). Patients diagnosed with early rectal cancer (defined by clinical stage T3/4, N0) who completed CRT followed by surgery were enrolled in this retrospective study. To evaluate the role of AC, we analyzed the risk of recurrence and survival based on clinicopathologic parameters and adjuvant chemotherapy. Of the 112 patients, 11 patients (9.8%) experienced recurrence and five patients (4.8%) died. In a multivariate analysis, circumferential resection margin involvement (CRM+) on magnetic resonance imaging at diagnosis, CRM involvement following neoadjuvant therapy (ypCRM+), tumor regression grade ($\leq$G1) and no-AC were considered poor prognostic factors for recurrence free survival (RFS). In addition, ypCRM+ and no-AC were associated with poor overall survival (OS) in the multivariate analysis. AC including 5-FU monotherapy demonstrated the benefits of reduced recurrence and prolonged survival in clinical stage II rectal cancer, even in pathologic stage following neoadjuvant therapy (ypStage) 0-I. Further prospective studies are needed to verify the benefit of each regimen of AC and the development of a method that can accurately predict CRM status before surgery, and a vigorous treatment that can induce CRM non-involvement (CRM$-$) should be considered even in early stages of rectal cancer.

Key Words: *Rectal Neoplasms; Chemotherapy, Adjuvant; Chemoradiotherapy; Prognosis*

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INTRODUCTION

Early rectal cancers of clinical T1/2 stage without lymph node metastasis (stage I) can be cured only by surgery. However, in more advanced stages including some stage II, the disease is difficult to cure with surgery alone, because of high risk of local recurrence due to the rectum's close proximity to pelvic structures, and technical difficulties in obtaining a wide surgical margin. Thus, in patients with locally advanced rectal cancer (LARC) as defined by $\geq$T3/N+ or additional risk factors such as tumor location, depth of mesorectal invasion, extramural vascular invasion (EMVI), or mesorectal fascia threatening/involvement, preoperative chemoradiotherapy (CRT) is routinely delivered to reduce the risk of local tumor recurrence.[1-3] In spite of these efforts, the risk of developing extra-pelvic metastasis still remains, in approximately 25% of patients.[4] To eradicate micrometastasis and circulating tumor cells that cannot be adequately removed by preoperative CRT, postoperative adjuvant chemotherapy (AC) has been used. Based on this unmet need and numerous randomized trials, it is now clear that compared with postoperative adjuvant CRT, preoperative CRT followed by AC yields significantly lowered local recurrence rates, lessened acute long-term toxicity and enabled a higher rate of sphincter-saving surgery, thereby improving quality of life of the patient and disease-free survival.[5]

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While the benefits of AC for colon cancer have been demonstrated with robust results in each stage, treatment strategies related to postoperative AC have not been sufficiently studied in rectal cancer.[6-8] One of the reasons for this paucity of research is that since CRT is performed before surgery in rectal cancer, it is not clear if the decision of performing AC should be based on the clinical stage (at diagnosis) or pathologic stage (after surgery). In addition, high-risk factors, which are well known in colon cancer, can be altered or be difficult to interpret after CRT. Despite these differences, AC is currently recommended for patients with LARC using regimens provided by the results of an adjuvant trial in colon cancer.[9,10] Recently, an Oxaliplatin-Based Adjuvant Chemotherapy for Rectal Cancer After Preoperative Chemoradiotherapy (ADORE) study including of 321 patients with ypStage II (T3-4N0) or III (ypT any N1-2) showed the effectiveness of FOLFOX (oxaliplatin plus infusional fluorouracil and leucovorin) for AC, compared to 5-FU and leucovorin in terms of disease-free survival (DFS).[11] Based on this study, FOLFOX has been suggested as a standard treatment for LARC, such as stage II or III after preoperative CRT followed by surgery. However, the superiority of FOLFOX was not demonstrated in the ypStage II in subgroup analysis. It suggests that the role of AC or optimal AC regimen in early rectal cancer should be redefined for improving survival and avoiding toxicity.

Therefore, this study was conducted to analyze the effect of AC on survival outcome in early rectal cancer based on clinicopathologic factors, confining to clinical stage II rectal cancer.

MATERIALS AND METHODS

1. Patients and treatment

Data from patients who underwent preoperative CRT followed by curative total mesorectal excision (TME) at Chonnam National University Hwasun Hospital (October 2015 to December 2019) were retrospectively reviewed. Patients who met the following criteria were included in this retrospective study: patients who were histologically diagnosed with adenocarcinoma of the rectum and clinically diagnosed with stage II (T3 or T4 without lymph node invasion) of the cancer. For clinical staging work-up, rectal magnetic resonance imaging (MRI) and chest/abdominopelvic computed tomography (CT) were examined before preoperative CRT. CRT was performed following a standard regimen of oral administration of capecitabine (825 mg/m^2) twice on days of irradiation concurrently with radiotherapy. Radiotherapy was administered once a day at 1.8 Gy/fraction per day, 5 days per week for a total dose of 45-50.4 Gy in 25-28 fractions. Six to eight weeks after the completion of preoperative CRT, follow up rectal MRI and curative surgery was performed. Postoperative management was performed by selecting among observation (no-AC), 5-FU/capecitabine or FOLFOX according to patient's condition. Thereafter, the patients received regular examination of the chest/abdomen every 6 months to monitor recurrence until 5 years after surgery.

This study was approved by the Chonnam National University Hwasun Hospital Institutional Review Board for the use of information obtained from patient records (CUNHH-2021-005).

2. Clinicopathologic analysis with survival outcomes

Clinicopathologic data, including age, sex, tumor location, tumor size, histological grade, lymphovascular invasion (LVI), and perineural invasion (PNI) were collected from medical and pathological records. Tumor response after CRT was described based on the Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1).

The pathological response to preoperative CRT was evaluated according to the modified Dworak tumor response grading (TRG) system as follows: grade 1, dominant tumor cell mass ($>50\%$) with obvious fibrosis or no regression; grade 2, dominantly fibrotic changes with few tumor cells or groups; grade 3, very few tumor cells (one or two microscopic foci <0.5 cm in diameter); and grade 4, complete response, no tumor cells, only fibrotic mass or acellular mucin pools.[12] Tumor stage was determined based on the 7th Edition of American Joint Committee on Cancer (AJCC) stating system.

The neoadjuvant rectal (NAR) score was calculated for each patient based on protocol used by George et al.[13]. The calculation formula, $[5\times pN-3(cT-pT)+12]^2/9.6$, incorporates cT, ypT, and ypN stage information, applying discrete weighting values for each staging category. The score values of the study population were categorized as low (<8), intermediate (8-16), and high (>16), following the validation results of the NSABP-03 and CAO/ARO/AIO-04 trials.[14]

3. Statistics

Association analyses among clinicopathological parameters were performed using the chi-square test and Fisher's exact test. Survival analyses were calculated using the Kaplan-Meier method and curves were compared using the log-rank test. Overall survival (OS) was defined as the time from the date of surgery to the date of death. RFS was defined as the time from the date of surgery to the date of recurrence or death, whichever occurred first. If neither event occurred by the time of analysis, the patient was censored. Factors associated with OS and recurrence free survival (RFS) were identified by univariate and multivariate Cox proportional hazard regression models with hazard ratios (HRs) and 95% confidence intervals (CIs). All variables from univariate analysis with p-values <0.1 were incorporated in the multivariate Cox hazard regression model with a step-wise forward procedure. Statistical analyses were performed using SPSS version 24.0 (IBM Corp., Armonk, NY, USA) All p-values were two-sided, and p-values <0.05 were considered statistically significant.

RESULTS

1. Patient characteristics

Of the 151 patients who met the inclusion criteria from October 2015 to December 2019, 23 patients were excluded due to insufficient pathologic or radiologic reports, and 16 patients were lost to regular follow-up. As a result, the data from 112 patients were analyzed for this study (Fig. 1). There were no statistical differences in demographic and clinical characteristics according to adjuvant chemotherapy or not except for age.

Baseline demographic and clinical characteristics of the patients in RFS and OS are presented in Table 1. The median age was 71 years (range 34-84 years), and 74 patients (66%) were men. All patients presented with histologically proven adenocarcinoma of the rectum, and 48 patients (43%) presented with lower rectal cancer. 102 patients (91%) presented with clinical T3 tumors without lymph node invasion. Among these patients, the circumferential resection margin (CRM) involvement following neoadjuvant therapy (ypCRM+) and the extramural vascular invasion (EMVI)+ groups included 18 (16%) and 7 (6%) patients, respectively.

2. Tumor response after preoperative CRT and pathologic outcomes after surgery

As discussed in methods, all patients included in this study completed both chemotherapy and radiotherapy. After preoperative CRT, overall response rate to treatment was 98% including 44% of complete response (CR) based on RECIST criteria.

After surgery, a total of 70 patients (62.5%) were downstaged and 30 patients (26.8%) among them showed pathologic CR (ypCR). Whereas, 12 patients (10.7%) were upstaged (cT3N0→ypT4N0 or pTxN1). ypCRM+ was shown in 7 patients (6.3%). The CRM status on MRI before preoperative CRT (preCRM) showed a similar trend to ypCRM (p-value=0.081). Classifications lower than TRG 2 ($>50\%$ of viable tumor cells) were shown in 11 patients (9.8%) while a NAR score of more than 16 were shown in 11 patients (9.8%). However, there was no statistical association between the TRG and NAR scores.

3. Pattern of failure and survival outcomes

The median follow-up duration was 48.3 months (range 12.4-76.3 months). Eleven patients (9.8%) experienced recurrence: locoregional recurrence occurred in 3 patients (2.7%) and distant metastasis occurred in 8 patients (7.1%). Among these patients, three received curative surgical resection and are alive now without recurrence. At the time of data analysis, 5 patients had died and 3 patients were receiving palliative chemotherapy. 3Y-RFS was 95.1% (95% CI, 95.057-95.143) and 5Y-OS was 91.7% (95% CI, 91.618-91.782). Median RFS and OS were not reached at the end of follow-up.

4. Survival analysis according to clinicopathologic parameters

In univariate analysis, tumor location (lower), preCRM+, ypCRM+, TRG (G1) and no-AC were significantly associated with poor RFS. Among these, preCRM+, ypCRM+, TRG (G1) and no-AC were significant prognostic factors for recurrence in the multivariate analysis. In terms of overall survival, ypCRM+ and non-AC were significant poor prognostic factors in both univariate and multivariate analysis (Table 2).

Although there was no statistical significance, recurrence tended to be more common in the low TRG group (p-value=0.076, 7.9% in TRG ≥ 2 vs. 27.3% in TRG 1). High risk features such as tumor grade, PNI and LVI were not associated with either RFS or OS in this study. However, the detection rate of PNI was higher in ypStage II-III (23.4%) than ypStage 0-I (6.5%, p-value=0.022).

The most important factor in this study, ypCRM+, showed a significant relationship with T4 stage at diagnosis (cT4, p-value=0.015). In the survival analysis incorporating T stage and preCRM status, cT4 with preCRM+ showed significantly shorter RFS than others, followed by

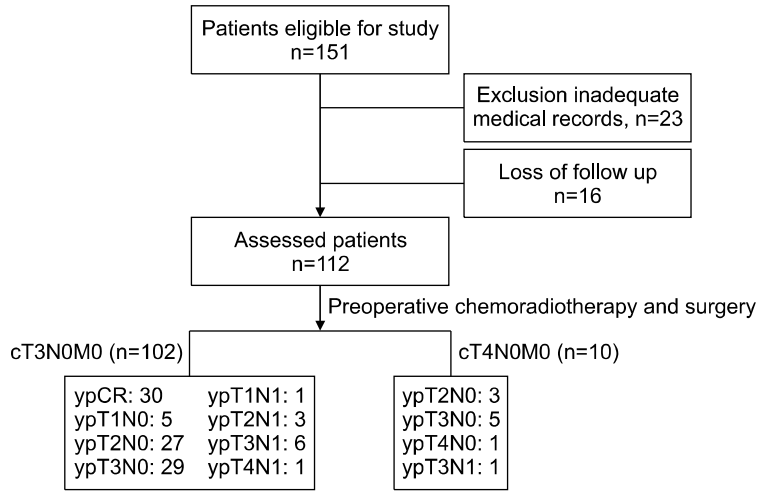

FIG. 1. Diagram of patient selection and treatment outcomes.

Table 1. Univariate analysis of clinicopathologic factors for RFS and OS

	N	RFS	p-value	OS	p-value
		Hazard ratio (95% CI)		Hazard ratio (95% CI)	
Age, years			0.922		0.218
70	53				
>70	59	1.061 (0.322-3.496)		2.972 (0.441-35.733)	
Sex			0.815		0.052
Male	74	1.076 (0.581-1.992)		0.107 (0.012-0.975)	
Female	38				
Site			**0.030**		0.118
Upper-mid	64				
Lower	48	4.361 (1.154-16.472)		5.736 (0.641-51.339)	
Baseline MRI					
cT stage					
cT3	102				
cT4	10	3.088 (0.653-14.605)	0.155	2.958 (0.326-26.830)	0.335
CRM					
No	94				
Yes	18	4.606 (1.383-15.335)	**0.013**	4.208 (0.699-25.314)	0.117
EMVI					
No	73				
Yes	39	1.794 (0.539-5.974)	0.341	1.159 (0.193-6.943)	0.872
CRT					
CR	49				
Non-CR	63	2.719 (0.576-12.830)	0.206		
After surgery					
Grade					
poorly	2	3.156 (0.668-14.915)	1.147	52.712 (0.035-7833.918)	0.287
PNI+	15	2.101 (0.263-16.795)	0.484	0.039 (0.000-46903.81)	0.557
LVI+	3	1.845 (0.189-18.022)	0.5991	0.048 (0.000-3104.00)	0.807
ypT stage					
ypT0-2	69				
ypT3-4	43	1.851 (0.557-6.156)	0.315	1.100 (0.183-6.604)	0.917
ypN stage					
ypN0	100				
ypN1-2	12	2.255 (0.533-9.543)	0.269	1.825 (0.203-16.415)	0.592
ypStage					
0-I	65				
II-III	47	1.574 (0.475-5.215)	0.458	1.074 (0.179-6.445)	0.938
ypCR					
CR	30				
non-ypCR	92	3.092 (0.391-24.431)	0.285	31.839 (0.005-19409.842)	0.436
ypCRM+					
No	105				
Yes	7	26.588 (5.191-136.182)	**0.000**	43.043 (5.639-328.584)	**0.000**
TRG, G1	11	5.609 (1.435-21.929)	**0.013**	3.157 (0.348-28.651)	0.307
NAR score, >16	11	2.448 (0.574-10.432)	0.226	2.003 (0.222-18.079)	0.536
Adjuvant chemotherapy					
None	27	2.549 (1.348-4.820)	**0.004**	18.941 (2.086-171.956)	**0.009**
Yes	85				

Bold font indicates significance. cT: clinical T stage, CRM: circumferential resection margin, EMVI: extramural vascular invasion, CRT: chemoradiotherapy, CR: complete response, PNI: perineural invasion, LVI: lymphovascular invasion, yp: pathologic data after systemic treatment, TRG: tumor regression grade, NAR score: neoadjuvant rectal score, RFS: recurrence free survival, OS: overall survival, CI: confidence interval.

TABLE 2. Mutivariate analysis of clinicopathologic factors for RFS and OS

	RFS Hazard ratio (95% CI)	p-value	OS Hazard ratio (95% CI)	p-value
Site, Lower	2.217 (0.528-9.306)	0.277		
Baseline MRI, CRM+	13.119 (2.065-83.329)	0.006		
ypCRM+	28.092 (4.354-181.252)	0.000	16.712 (2.223-125.608)	0.006
TRG, G1	12.908 (2.127-78.349)	0.005		
No Adjuvant chemotherapy	24.358 (3.226-183.901)	0.002	12.892 (1.285-129.339)	0.030

CRM: circumferential resection margin, yp: pathologic data after systemic treatment, TRG: tumor regression grade, RFS: recurrence free survival, OS: overall survival, CI: confidence interval.

cT3 with preCRM+, cT4 with preCRM- and cT3 with CRM- (p-value=0.026). Regarding tumor location, the incidence of preCRM+ was higher in lower rectal cancer (22.9%) than mid or upper rectal cancer (10.9%), but there was no statistical significance.

5. Survival outcomes according to adjuvant chemotherapy

There was no significant difference in the selection of AC regimen according to clinical parameters such as age, tumor location and stage.

Patients showing more than TRG G2 showed significant benefit in RFS (p-value $<$ 0.001) and OS (p-value=0.004). Of patients with ypStage 0-I (n=64), 16 (25%) patients did not receive AC, 47 patients (73%) received 5-FU and one patient (2%) received FOLFOX chemotherapy. Of patients with ypStage II-III (n=46), 9 patients (19.6%) did not receive AC, 26 patients (56.5%) received 5-FU and 11 patients (23%) received FOLFOX chemotherapy. There was a significant difference in the selection of a FOLFOX regimen as an AC in ypStage 0-I and ypStage II-III (p-value=0.001). On comparing the group of patients who received AC with those who did not, RFS and OS were improved in AC group both in ypStage 0-I (p-value=0.007 and p-value=0.008, respectively) and ypStage II-III (p-value=0.042 and p-value=0.006, respectively). Next, we reanalyzed the treatment outcomes according to each regimen. As shown in Fig. 2, both 5-FU and FOLFOX improved RFS (p-value=0.027) and OS (p-value=0.030) in ypStage 0-I. In ypStage II-III, AC increased OS regardless of the type of regimen, but there was a slight difference in RFS according to regimen.

DISCUSSION

In this study, we showed the benefit of AC in clinical stage II rectal cancer regardless of clinicopathologic findings. FOLFOX or capecitabine plus oxaliplatin (CapeOX) usage after preoperative CRT followed by surgery is recommend as the standard of care for LARC of clinical stage T3, N any with clear CRM by the practice guidelines, such as those of the National Comprehensive Cancer Network (NCCN).

Nevertheless, the question of postoperative treatment for early rectal cancer remains unresolved. What is the importance of clinical stage before CRT (cTNM) to determine the prognosis in LARC? How should patients with ypStage 0-I be treated? Do the known high-risk features of colon cancer such as tumor grade, PNI, or LVI have similar significance in early stages of rectal cancer? Previous reports showed that AC was associated with improved OS in LARC, even in patients with ypCR after preoperative CRT.[9,15] However, the level of evidence was low due to the absence of randomized trial in patients with pCR; further high-quality trials are required to confirm findings. In addition, there is general concern about the need to avoid overtreating for early-stage tumors that do not require treatment.[7,8,16,17] Thus, it is important to redefine the benefits of AC for each stage of rectal cancer and to stratify patients by identifying risk factors.

Previously, we reported the prognostic impact of PNI in rectal cancer after preoperative CRT. In this study, the detection rate of PNI was 28.8% and multivariate analysis revealed that PNI was a poor independent prognostic factor for both DFS and OS. Specifically, PNI was associated with more aggressive tumor features (T0-T2 vs. T3-T4, $p < 0.001$) in multivariate analysis.[18] This result suggested that PNI is a marker implicating the aggressive tumor stage; and thus, it could be a prognostic factor for rectal cancer after surgery. Contrary to this result, the present study showed no significant effect of PNI or LVI on survival outcomes. As mentioned in results, PNI was detected in 15 patients (13.4%) and LVI was detected in only 3 patients (2.7%). The low detection rate of LVI may be related to the clinical node-negative patient population and the effect of preoperative CRT. Although the present study showed a higher expression rate of PNI in ypStage II-III (23.4%) than in ypStage 0-I (6.5%), there was no statistical significance in the prognosis. It suggests that known high risk factors may have limited significance in stage II rectal cancer which needs to be validated.

According to NAR score, there was no prognostic impact in our study, but it was a significant prognostic factor for RFS and OS in stage III patients in the same cohort population (data was not shown). That is, the NAR score has prognostic significance in stage III patients with LN metastasis, but suggests that there are limitations in stage II patients without LN metastasis.

Similar to other reports, ypCRM was found to be the most important prognostic factor for recurrence and survival in

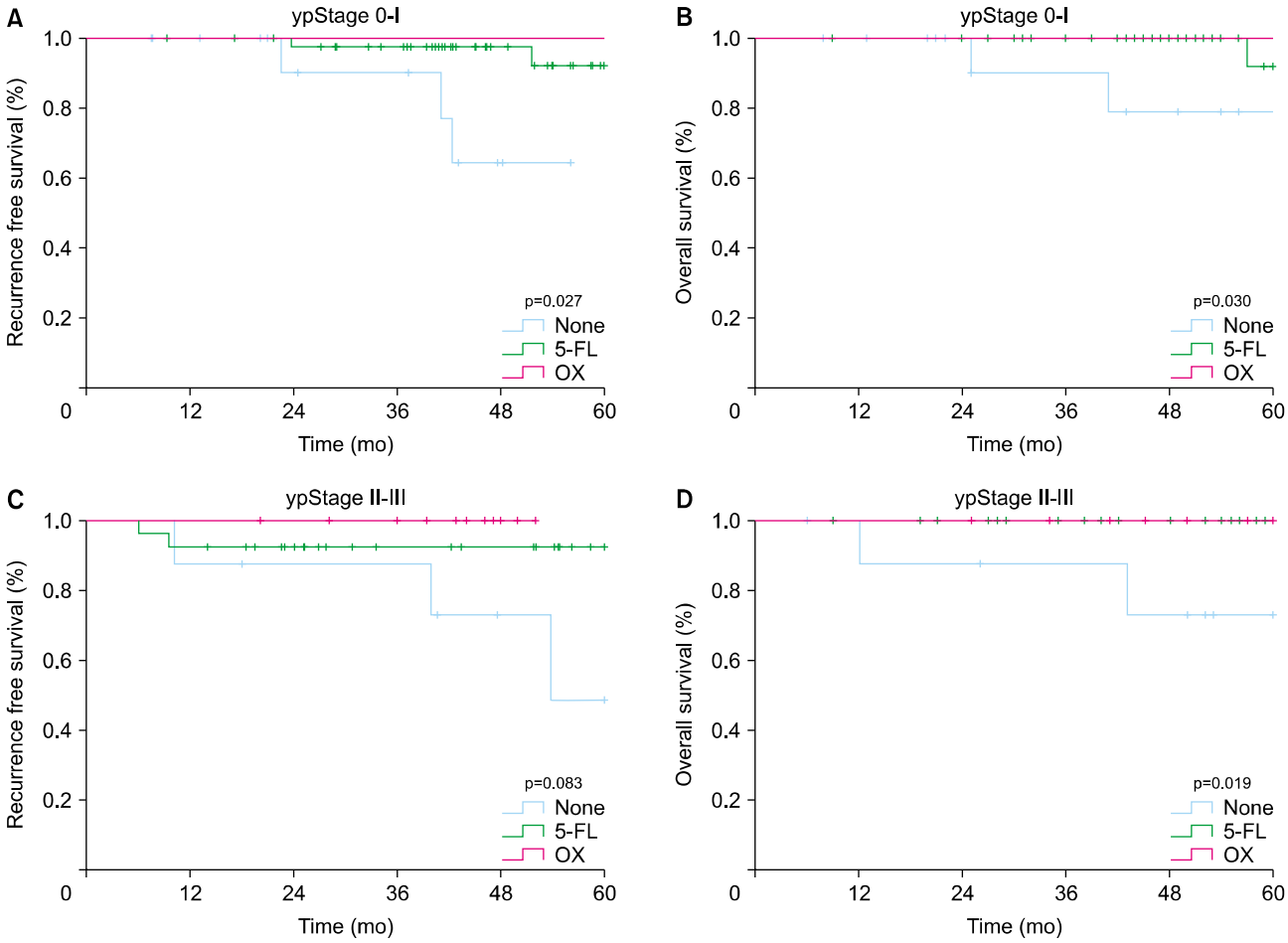

FIG. 2. Kaplan-Meier curves of recurrence free survival (A, C) and overall survival (B, D) based on adjuvant chemotherapy regimen according to ypStage. 5-FU: oral capecitabine or 5-FL/leucovorin, OX: oxaliplatin containing regimen.

our study, and both preCRM+ and ypCRM+ were independent prognostic factors for RFS in the multivariate analysis; thus, patients should carefully consider surgery as they can be candidates for total neoadjuvant treatment (TNT). This result could be associated with the inaccuracy of tumor mass calculations due to radiation effects. Unfortunately, CRM status on MRIs after CRT (before surgery) had a lack of statistical significance for survival in our study (p=0.07 in RFS). As a related study, Bae et al.[19] reported the usefulness of follow-up MRI for the prediction of pCR after neoadjuvant CRT in patients with clinical T1/T2 rectal cancer. In addition, as studies on radionomic analysis to improve the prediction of pCR have recently been reported, further imaging methods may help select high-risk patients.[20-22]

The most valuable result in our study is the demonstration of the usefulness of AC not only in ypStage II-III but also in ypStage 0-I. In addition, unlike ypStage II-III which requires a oxaliplatin containing regimen, patients with ypStage 0-I showed significant improved RFS and OS with 5-FU alone comparable to FOLFOX. In fact, age and comorbidities were major determinants for the compliance of AC after surgery, in practice. The median age of this study population was 71 years including of 39 patients (34.8%) aged 75 years or older. Thus, 5-FU monotherapy could be suggested as an alternative AC for FOLFOX in patients with ypStage 0-I.

Although meaningful results were obtained as described above, our study has several shortcomings. The small sample size's effect on stratification of each risk factor is a major limitation. But, given the analysis in the specific group of clinical T3/T4 tumors without LN metastasis, these findings can provide physicians with some guidance regarding management options and additional evidence to set up standardized guidelines for such a patient population in future prospective studies.

AC after surgery showed benefits of reduced recurrence rates and prolonged survival in patients with clinical stage II rectal cancer regardless of ypStage. In addition, 5-FU monotherapy showed improved survival outcomes in ypStage 0-I, so it may be considered as an AC to avoid toxicity related to oxaliplatin. Finally, there is a need for intensive research on methods that can detect CRM status before surgery or converting CRM-negative in LARC.

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CONFLICT OF INTEREST STATEMENT

None declared.

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