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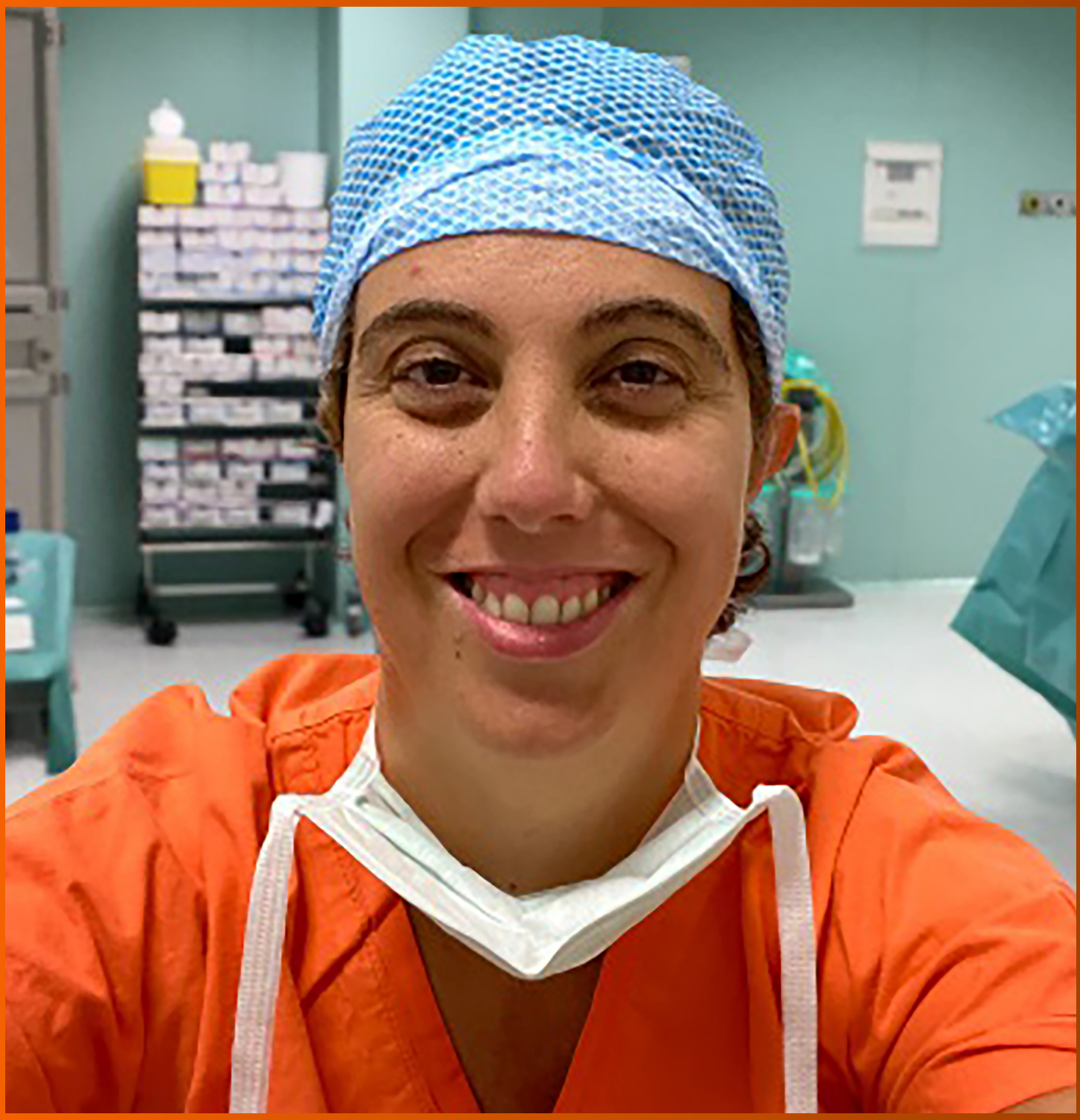

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ABOUT COVER

AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Surgery* (*WJGS*, *World J Gastrointest Surg*) is to provide scholars and readers from various fields of gastrointestinal surgery with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

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ORIGINAL ARTICLE

Retrospective Study

Evaluating the benefit of adjuvant chemotherapy in patients with ypT0–1 rectal cancer treated with preoperative chemoradiotherapy

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Abstract

BACKGROUND

Adjuvant chemotherapy (ACTx) is recommended in rectal cancer patients after preoperative chemoradiotherapy (PCRT), but its efficacy in patients in the early post-surgical stage who have a favorable prognosis is controversial.

AIM

To evaluate the long-term survival benefit of ACTx in patients with ypT0–1 rectal cancer after PCRT and surgical resection.

METHODS

We identified rectal cancer patients who underwent PCRT followed by surgical resection at the Asan Medical Center from 2005 to 2014. Patients with ypT0–1 disease and those who received ACTx were included. The 5-year overall survival (OS) and 5-year recurrence-free survival (RFS) were analyzed according to the status of the ACTx.

RESULTS

Of 520 included patients, 413 received ACTx (ACTx group) and 107 did not (no ACTx group). No significant difference was observed in 5-year RFS (ACTx group,

Data sharing statement: Data are available upon reasonable request. We may be able to share de-identified participant data with researchers following the publication of this manuscript. Requests for data should be directed to the corresponding author. Data sharing will need to be approved by third-party data providers.

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87.9% *vs* no ACTx group, 91.4%, $P = 0.457$) and 5-year OS (ACTx group, 90.5% *vs* no ACTx group, 86.2%, $P = 0.304$) between the groups. cT stage was associated with RFS and OS in multivariate analysis [hazard ratio (HR): 2.57, 95% confidence interval (CI): 1.07–6.16, $P = 0.04$ and HR: 2.27, 95%CI: 1.09–4.74, $P = 0.03$, respectively]. Furthermore, ypN stage was associated with RFS and OS (HR: 4.74, 95%CI: 2.39–9.42, $P < 0.00$ and HR: 4.33, 95%CI: 2.20–8.53, $P < 0.00$, respectively), but only in the radical resection group.

CONCLUSION

Oncological outcomes of patients with ypT0–1 rectal cancer who received ACTx after PCRT showed no improvement, regardless of the radicality of resection. Further trials are needed to evaluate the efficacy of ACTx in these group of patients.

Key Words: Rectal neoplasm; Adjuvant chemotherapy; ypT0-1; Radical resection; Local excision

Core Tip: Adjuvant chemotherapy (ACTx) is administered based on the clinical stage of rectal cancer after preoperative chemoradiotherapy (PCRT), regardless of post-treatment pathologic stage. Prognosis differs according to post-treatment pathologic stage or regression grade. Adjuvant treatment may be administered based on prognostic influence. Patients with ypT0-1 rectal cancer with favorable oncologic outcomes were included. Since local excision (LE) frequency has increased, ACTx effects in these patients need to be studied. We included patients who underwent LE. ACTx in patients with ypT0-1 rectal cancer after PCRT and LE did not exert benefits in terms of overall survival and recurrence-free survival.

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INTRODUCTION

The current guidelines recommend the use of adjuvant chemotherapy (ACTx) in patients who have undergone preoperative chemoradiotherapy (PCRT) and surgical resection based on the clinical stage before PCRT[1]. However, the efficacy of ACTx, regardless of the patients' pathological findings, is controversial[2]. Previous studies have reported an improvement in the oncological outcomes of rectal cancer patients who underwent PCRT, total mesorectal excision (TME), and ACTx[3-5]; the outcomes differed according to the postoperative pathological stage or the tumor regression grade[6,7] rather than the pre-PCRT clinical stage. Therefore, tumor regression grade and post-surgical stage have been considered predictors of oncological outcomes of ACTx[8].

Patients with good response to PCRT have a favorable prognosis, and the 5-year recurrence-free survival (RFS) of patients with yp stage 0 and 1 disease after PCRT is > 90%[9,10]. Considering the risks of ACTx such as toxicity and financial burden[11,12], limited information is available regarding the oncological benefit of ACTx in patients with early yp stage 0 and 1 diseases[13]. Recent studies analyzing the oncological benefit of ACTx in patients who achieved a pathological complete response have reported inconsistent results[14-18]. Therefore, it is imperative to analyze the survival benefit of ACTx in patients in the early post-surgical stage who have a good prognosis. Hence, this study aimed to evaluate the long-term survival benefit of ACTx in patients with ypT0–1 disease after PCRT and surgical resection.

MATERIALS AND METHODS

Patients

We initially identified 5207 rectal cancer patients who underwent PCRT followed by surgical resection [radical resection or local excision (LE)] between January 2005 and December 2014 at the Asan Medical Center, Seoul, South Korea. Of the patients who underwent PCRT, 42 who were lost to follow-up and 1341 with ypT2–4 or ypTx disease were excluded. Patients who received ACTx postoperatively were categorized into the ACTx group, while those who did not receive ACTx postoperatively were categorized into the no ACTx group (Figure 1). This study was approved by the Institutional Review Board of (registration No. 2017-1114), which waived the requirement for obtaining an informed consent due to the retrospective nature of the study.

PCRT and surgery

For patients who opted to receive PCRT, a radiation dose of 45–50.4 Gy was delivered in 20–28 fractions (1.8–2.0 *per* fraction) to a target volume including the primary tumor, perirectal adipose tissue, lateral pelvis, and presacral lymph node (LN) during the PCRT treatment period. Concurrent chemotherapy consisted of either two cycles of intravenous bolus injection of 5-fluorouracil (5-FU, 375 mg/m^2/d) and leucovorin (20 mg/m^2/d) (FL) or oral administration of capecitabine (825 mg/m^2) twice daily. Other agents such as oxaliplatin, TS-1, and temozolomide were used as a combination therapy in some patients.

Surgical resection was performed 6–12 wk after the completion of radiation therapy. Radical surgical resection was performed according to the principles of TME. For the LE of the tumor, transanal LE, transanal minimally invasive surgery, or full thickness excision was performed.

ACTx was recommended in all medically fit patients who underwent PCRT. The recommended adjuvant regimen consisted of four cycles of 5-FU and leucovorin (FL) monthly or six cycles of capecitabine.

Surveillance and oncological outcomes

All patients underwent postoperative follow-up, which consisted of physical examination, serum carcinoembryonic antigen measurement, chest radiography, and abdominal, pelvic, and chest computed tomography (CT) every 3–6 mo. Most patients underwent colonoscopy between 6 mo and 1 year postoperatively and every 2–3 years thereafter. Recurrence was determined according to the radiological or histopathological findings. Local recurrence was defined as the presence of a suspicious lesion in the areas contiguous to the bed of the primary rectal resection or the site of anastomosis, while distant metastasis was defined as the presence of any recurrence in a distant organ or dissemination to the peritoneal surface. RFS was measured from the date of surgery to the date of detection of the first recurrence or death.

Patients who underwent LE were followed up every 3 mo for the first 1–2 years postoperatively and every 6 mo thereafter. Physical assessment with digital rectal examination and laboratory tests including sigmoidoscopy were performed every 3 mo for the first 1–2 years and every 6 mo for the next 3–4 years for a total of 5 years. Full colonoscopy was performed within 1 year after surgery and every 2–3 years thereafter. Abdominopelvic and chest CT was performed every 6 mo for 5 years.

Statistical analysis

Categorical variables were compared using the chi-square test, while normally distributed continuous data were analyzed using the Student's *t*-test. Survival curves were constructed using the Kaplan–Meier method and compared using log-rank tests according to the status of ACTx. The associations between the clinical factors and RFS were determined using the Cox proportional hazard regression analysis. Statistical significance was assumed at a level of 5%. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY, United States).

RESULTS

Clinicopathological characteristics of patients

A total of 520 patients were enrolled. The mean (± SD) age was 59.1 ± 10.5) years.

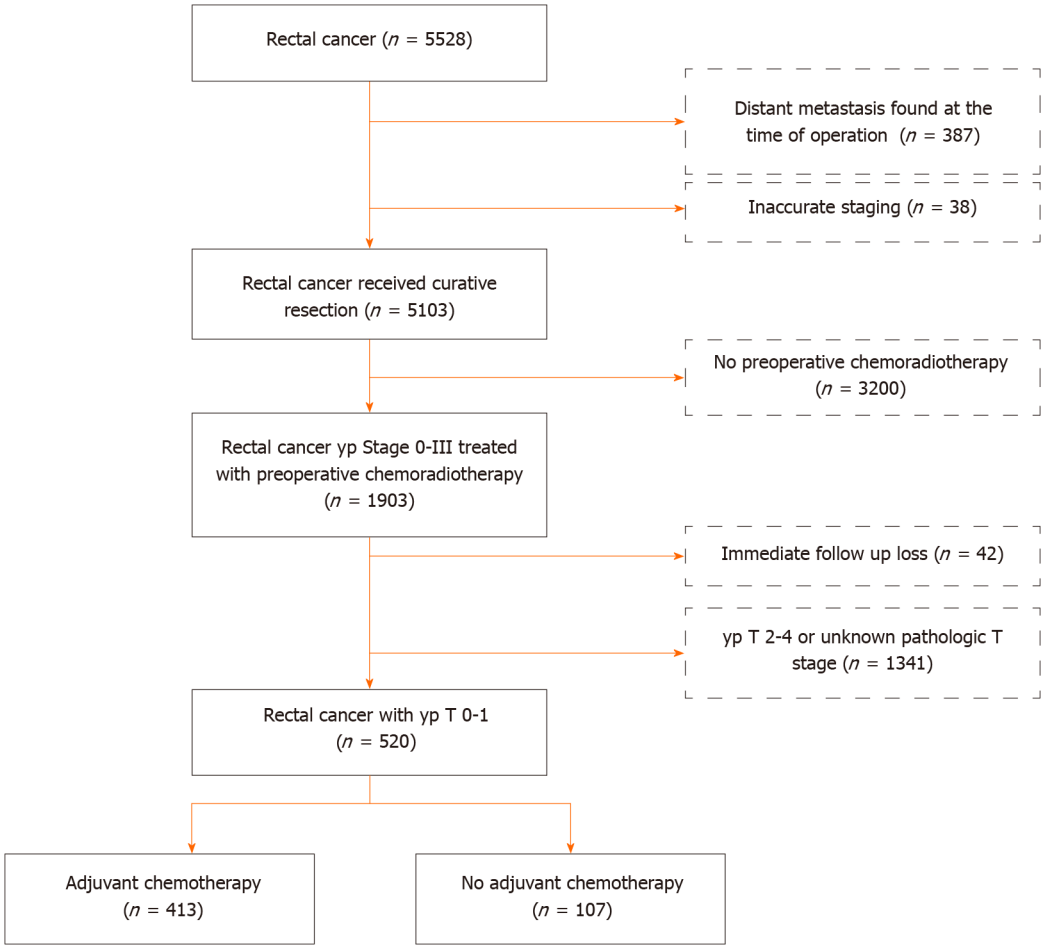

Figure 1 CONSORT diagram. Inclusion of patients.

Approximately 59.4% patients were men, and 85% patients underwent radical resection. The mean follow-up duration was 71.0 ± 32.6 mo. In the ACTx and no ACTx groups, the proportion of patients with cT3–4 and cN+ disease was higher than that of patients with cT1–2 and cN− disease. The ACTx group had a higher proportion of patients with advanced cT and cN disease compared with the no ACTx group. There was no significant difference in ypT stage between both groups. LN retrievals were evaluated in patients who underwent radical resection. The mean number of examined LNs and proportion of patients with ypN stage were similar in both groups (Table 1).

Oncological outcome according to ACTx

The recurrence rates were significantly different according to the status of ACTx (P = 0.009). The ACTx group had a recurrence rate of 10.4% (43/413), and most patients had distant metastasis (9.7%, 40/43). The most common site of metastasis in the ACTx group was the lung (57.5%). The no ACTx group had a recurrence rate of 7.4%, which was significantly lower than that of the ACTx group (P = 0.009). Distant LNs were the most common site of metastasis in the no ACTx group (Table 2). The 5-year RFS rates in the ACTx and no ACTx groups were 87.9% and 91.4%, respectively (P = 0.457), while the overall survival (OS) rates were 90.5% and 86.2%, respectively (P = 0.304). No significant difference was observed in the RFS and OS between the groups (Figure 2).

When the RFS and OS were analyzed by the type of surgery (radical resection or LE) according to the status of ACTx, no significant difference was observed with regard to the 5-year RFS in patients who underwent radical resection and LE between the ACTx group and the no ACTx group (radical resection: 90.3% *vs* 92.9%, P = 0.363; LE: 90.4% *vs* 89.6%, P = 0.996). Similarly, no significant difference was found regarding the 5-year OS in patients who underwent radical resection and LE between the ACTx group and the no ACTx group (radical resection: 93.7% *vs* 90.6%, P = 0.167; LE: 91.4% *vs* 90.7%, P = 0.945; Figure 3).

Table 1 Clinicopathological characteristics of the study patients

Variables		ACTx (*n* = 413)	No ACTx (*n* = 107)	*P* value
Age, mean ± SD, yr		58 ± 10.1	63.4 ± 11.0	< 0.001
Sex, *n* (%)				0.659
	Male	243 (58.8)	66 (61.7)	
	Female	170 (41.2)	41 (38.3)	
cT category, *n* (%)				< 0.001
	cT1–2	83 (20.1)	48 (44.9)	
	cT3–4	330 (79.9)	59 (55.1)	
cN category, *n* (%)				< 0.001
	cN-	65 (15.7)	34 (31.8)	
	cN+	348 (84.3)	73 (68.2)	
Type of surgery, *n* (%)				< 0.001
	Radical resection	378 (91.5)	64 (59.8)	
	Local excision	35 (8.5)	43 (40.2)	
Number of examined LNs, mean ± SD[1]		14.7 ± 6.9	14.6 ± 6.3	0.892
pT category, *n* (%)				0.099
	ypT0	294 (71.2)	67 (62.6)	
	ypTis–1	119 (28.8)	40 (37.4)	
pN category[1], *n* (%)				0.201
	ypN0	347 (91.8)	62 (96.9)	
	ypN+	31 (8.2)	2 (3.1)	
Lymphovascular invasion, *n* (%)		4 (1)	-	0.339
Follow-up duration mean ± SD, months		72.1 ± 33.0	66.4 ± 30.3	0.105

[1]Only for radical resection.
SD: Standard deviation; ACTx: Adjuvant chemotherapy; LN: Lymph node.

Risk factor associated with RFS and overall survival

In the univariate analysis, none of the risk factors were associated with RFS, including the administration of ACTx. In the multivariate analysis, cT3–4 stage was the only risk factor associated with RFS [hazard ratio (HR): 2.57; 95% confidence interval (CI): 1.07–6.16, $P = 0.04$]. Even in the subgroup analysis of patients with cT3–4 stage disease, ACTx was not associated with RFS (HR: 1.358, $P = 0.521$; Table 3). Apart from age, none of the risk factors were associated with OS in the univariate analysis. In contrast, cT stage was a significant risk factor for OS in the multivariate analysis (HR: 2.268, 95%CI: 1.09–4.74, $P = 0.03$). However, in the multivariate Cox regression analysis of the cT3–4 group, administration of ACTx was not a significant risk factor for OS (Table 4).

In patients undergoing radical surgical resection, ypN stage was a risk factor associated with RFS and OS. ypN+ stage was a risk factor for RFS in both the univariate and multivariate analyses (HR: 4.86, $P < 0.00$ and HR: 4.74, 95%CI: 2.39–9.42, $P < 0.00$, respectively). It was also confirmed as a risk factor for OS in the multivariate analysis (HR: 4.33, 95%CI: 2.20–8.53, $P < 0.00$). However, administration of ACTx was not associated with both RFS and OS in patients who underwent radical resection.

DISCUSSION

In this study, it was found that the ACTx did not improve the RFS and OS of patients with ypT0–1 rectal cancer who underwent PCRT and resection. In the subgroup

Table 2 Sites of initial recurrence according to the status of adjuvant chemotherapy

Variables	ACTx (*n* = 413)	No ACTx (*n* = 107)	*P* value
Recurrence, *n* (%)	43 (10.4)	8 (7.4)	
Type of recurrence, *n* (%)			0.009
Local recurrence	3 (0.7)	4 (3.7)	
Distant metastasis	40 (9.7)	4 (3.7)	
Sites of distant metastasis[1], *n* (%)			
Liver	8 (20)	1 (12.5)	
Lung	23 (57.5)	2 (25)	
Distant lymph nodes	6 (15)	1 (12.5)	
Bone	4 (10)	-	
Brain	1 (2.5)	-	
Ovary	1 (2.5)	-	

[1]Among patients with distant metastasis.
ACTx: Adjuvant chemotherapy.

Table 3 Risk factors associated with recurrence-free survival

	Univariate		Multivariate		
	HR	*P* value	HR	95%CI	*P* value
Adjuvant chemotherapy		0.459			0.608
No	1		1		
Yes	1.331		1.226	0.563–2.671	
Sex		0.582			
Male	1				
Female	1.77			0	
cT category		0.082			0.035
cT1–2	1		1		
cT3–4	2.031		2.565	1.06–6.156	
cN category		0.399			
cN−	1				
cN+	0.756				
Type of surgery		0.927			
Local excision	1				
Radical resection	1.038				
ypT stage		0.389			
ypT0	1				
ypTis–1	0.757				

HR: Hazard ratio; CI: Confidence interval.

analysis according to the type of resection, administration of ACTx was not associated with RFS and OS in patients who underwent LE and those who underwent radical resection. The significant risk factors for RFS and OS were cT stage and ypN stage in patients who underwent radical resection.

Table 4 Risk factors associated with overall survival

	Univariate		Multivariate		
	HR	*P* value	HR	95% CI	*P* value
Adjuvant chemotherapy		0.306			0.484
No	1		1		
Yes	0.729		0.797	0.422–1.504	
Age	1.047	0.001	1.052	1.022–1.084	0.001
Sex		0.156			0.213
Male	1		1		
Female	0.668		0.701	0.400–1.227	
cT category		0.122			0.029
cT1–2	1		1		
cT3–4	1.757		2.268	1.085–4.741	
cN category		0.475			
cN−	1				
cN+	1.296				
Type of surgery		0.692			
Local excision	1				
Radical resection	1.174				
ypT stage		0.612			
ypT0	1				
ypTis–1	0.861				

HR: Hazard ratio; CI: Confidence interval.

The present study included patients who underwent LE and those who underwent radical resection, while previous studies included patients who underwent either radical surgical resection or TME[14-18]. Tumor regression after neoadjuvant chemoradiotherapy has made it possible to perform LE according to the principles of TME for rectal cancer. The rate of LE after PCRT for rectal cancer has gradually increased over time[19]. Therefore, enrollment of patients who underwent LE after PCRT in this study may have a more practical importance in the clinical decision making, especially in patients with pathological downstaging. Furthermore, patients in this study had good adherence to ACTx; hence, the efficacy of ACTx was evaluated more precisely.

Previous studies have demonstrated that patients who achieve a pathological complete response after chemoradiation have a better prognosis than those who do not achieve a pathological complete response[20-22]. However, there was a lack of consensus in the efficacy of ACTx for good responders. Four randomized control trials in patients treated with PCRT followed by surgical resection failed to show an improvement in the oncological outcomes after ACTx and reported low accrual rates [4,23-25]. Despite the heterogeneity of the inclusion criteria, several retrospective studies have also reported that there is no significant oncological benefit of ACTx in low-risk patients with good response to PCRT[17,18,26-31]. Even in the long-term analysis of the 10-year cumulative cancer-specific survival, ACTx had no significant impact on patients with ypTis-2N0M0 stage in our previous report[32]. The possible risk factors associated with oncological outcomes are tumor regression grade[33], yp stage[27], cT stage and resection margin status[28], tumor grade[18], and residual tumor of ypT1–4[31].

Recent studies based on the National Cancer Database have shown contradictory results. One study showed that ACTx was associated with improved OS in patients who achieved a pathological complete response, and while another showed that ACTx was more beneficial in patients with pretreatment node-positive cancer than those without metastatic nodes[14,15]. Although these studies analyzed a large sample of

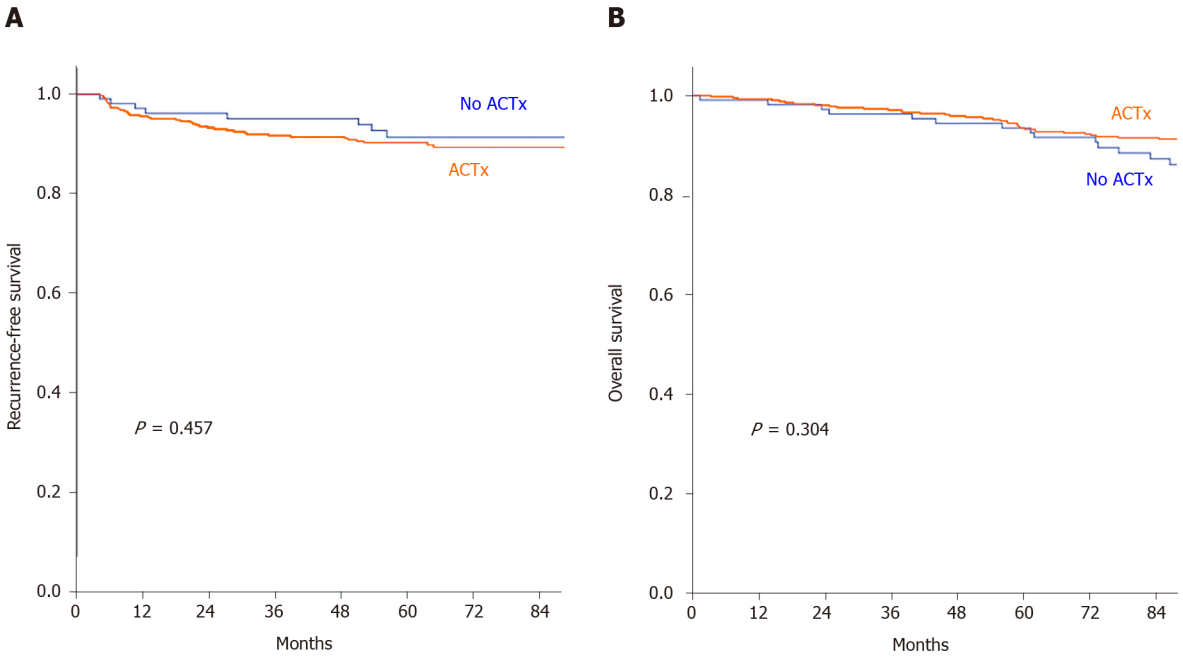

Figure 2 Oncological outcomes according to the status of adjuvant chemotherapy in patients with ypT0–1 rectal cancer after preoperative chemoradiotherapy. A: Recurrence-free survival; B: Overall survival. ACTx: Adjuvant chemotherapy.

patients, limited data on patient characteristics and clinical outcomes such as local recurrence and cancer-related death could obscure the results as an unmeasured confounding factor, worsened with the statistical features of propensity score matching[34]. Another large-scale study showed an association between the administration of ACTx and lower risk of death[35]; however, this study included all patients with stage II–III disease without analyzing the benefit of ACTx in each subgroup according to the ypT stage. A previous study showed additional benefit of ACTx; however, there was possible selection bias since younger and healthier patients were more likely to receive ACTx than older adults with comorbidities[16].

Hence, the results of the current study should be carefully interpreted as the analysis was performed in patients with ypN0 and ypN+ status. Although the LN status is one of the most important prognostic factors[36,37], we could not analyze the extent of nodal involvement as LN evaluation was limited during LE. In our study, the proportion of patients with ypT0–1N+ stage in the radical resection subgroup was 7.4% (33/442), which was similar to that reported in the previous study[36]; most of the patients with ypT0–1N+ stage received ACTx (93.9%, 31/33). Therefore, the influence of ACTx in patients with ypT0–1N+ could not be sufficiently evaluated in this study. Although the accuracy of the imaging diagnosis of LN metastasis is limited in current clinical practice, the rate of LE in rectal cancer patients who achieve complete or near complete regression of the primary tumor after PCRT has increased gradually[19]. Therefore, future studies should include not only patients who have undergone LE, but also those who have undergone radical resection considering the current clinical practice. In our study, among patients who had LE, 55.1% (43/78) did not receive ACTx, and the benefit of ACTx in ypT0–1 rectal cancer patients who underwent LE could be sufficiently evaluated.

The most common ACTx regimen administered in our study was 5-FU/Leucovorin or capecitabine. Long-term results of recent studies comparing the outcome of ACTx using different agents showed that patients with ypN1b and ypN2 disease benefited from FOLFOX rather than FL[8]. Patients enrolled in our study with early ypT stage who showed good response to PCRT seemed to have a lesser oncological benefit than those included in the abovementioned trial. LN metastasis remained a risk factor for RFS and OS even in patients with ypT0–1 disease. Therefore, further studies are needed to determine whether the same conclusion can be established when a more intense chemotherapy regimen is used.

This study has some limitations, which include the retrospective review of data from a single center and the small sample size. Selection bias resulted from the inclusion of patients who either underwent radical resection or LE. As current guidelines recommend ACTx to patients after PCRT and surgical resection regardless

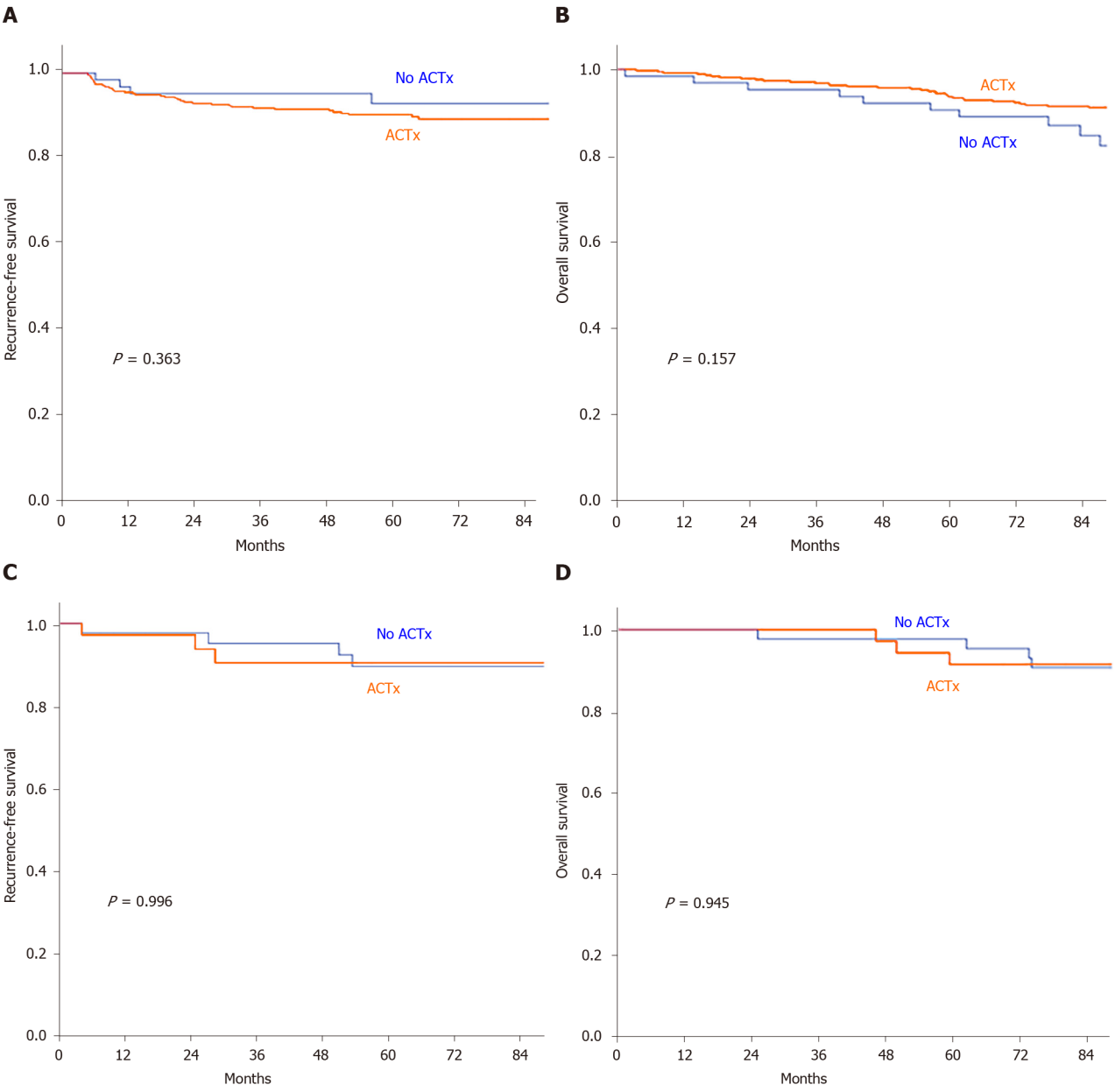

Figure 3 Oncological outcomes according to the status of adjuvant chemotherapy by the type of surgery. A: Recurrence-free survival (RFS) in patients treated with radical resection; B: Overall survival (OS) in patients who underwent radical resection; C: RFS in local excision (LE); D: OS in patients who underwent LE. ACTx: Adjuvant chemotherapy.

of post-treatment stage, few patients with ypT0–1N+ disease did not receive ACTx; hence, the comparison of patients with ypN+ disease who underwent radical resection between the ACTx group and the no ACTx group may not be sufficient. These limitations may influence the reliability of the results, which should be interpreted carefully.

Despite the study limitations, we demonstrated that there was no long-term survival benefit of ACTx in patients with ypT0–1 disease after PCRT regardless of the radicality of the surgery. Hence, the necessity of ACTx in patients with cT stage disease, a risk factor associated with RFS and OS, should be carefully reviewed in future studies.

CONCLUSION

In conclusion, ACTx in patients with ypT0–1 disease who had a good response to PCRT followed by surgical resection may not be beneficial in improving the oncological outcome. Routine ACTx based on the pretreatment clinical stage should be

carefully applied in the clinical setting considering the heterogenous oncological outcomes of patients at post-surgical stage.

ARTICLE HIGHLIGHTS

Research background

In rectal cancer patients after preoperative chemoradiotherapy (PCRT), adjuvant chemotherapy (ACTx) is recommended regardless of post-surgical stage.

Research motivation

It is controversial that ACTx improves the oncologic outcome in patients in the early yp stage expected to have a good prognosis.

Research objectives

This study is a retrospective study that aims to evaluate the survival benefit of ACTx in patients with ypT0–1 who underwent PCRT and surgical resection, including local excision.

Research methods

After identification of patients who received PCRT followed by surgical resection, analysis of the 5-yr recurrence-free survival (RFS) and overall survival (OS) of patients with ypT0–1 rectal cancer was performed according to the status of ACTx.

Research results

There was no significant difference in the 5-year RFS and 5-year OS between the two groups. In the multivariate analysis, cT stage was associated with RFS and OS. Also, ypN stage only analyzed in the radical resection group was associated with RFS and OS.

Research conclusions

Our study demonstrated no oncologic benefit of ACTx in patients with ypT0–1 rectal cancer after PCRT and surgical treatment regardless of the radicality of resection.

Research perspectives

In rectal cancer treated with PCRT, ACTx use, regardless of the final pathologic stage, needs to be carefully reconsidered. For ypT0-1 rectal cancer, ACTx did not show any oncologic benefit. Therefore, risk-stratified risk-benefit consideration is important for rectal cancer patients with good pathologic results after PCRT. Further studies with prospective, large-scale, and randomized trials are needed to evaluate the efficacy of ACTx in patients with early post-treatment stage rectal cancer who have a favorable prognosis.

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