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Original Article

Early recurrence after neoadjuvant chemoradiation therapy for locally advanced rectal cancer: Characteristics and risk factors

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SUMMARY

Background/objective: Some locally advanced rectal cancer (LARC) patients treated with neoadjuvant chemoradiotherapy (CRT) prior to total mesorectal excision (TME) show early recurrence with a short disease-free interval. This is unacceptable for patients and their families, necessitating re-evaluation of the treatment process. We aimed to evaluate the risk factors and prognostic impact of early recurrence in patients who received preoperative CRT (pCRT) followed by TME for LARC.

Methods: Of 714 patients who underwent curative resection after pCRT for LARC from January 2010 to December 2016, we included 139 who developed recurrence after resection. Patients were divided into an early recurrence group, diagnosed <12 months after primary surgery, and a late recurrence group, diagnosed ≥12 months after primary surgery.

Results: Forty-nine patients experienced early recurrence and 90 experienced late recurrence. Multivariate analysis revealed that tumor regression grade (hazard ratio [HR] 2.962, 95% confidence interval [CI] 1.434–6.119, P = 0.003) and positive ypN stage (HR 2.110, 95% CI 1.144–3.892, P = 0.017) correlated with early recurrence. The 5-year overall survival rates for early and late recurrences were not significantly different (P = 0.121).

Conclusion: In patients with early recurrence after pCRT followed by TME, tumor regression grade and ypN stage positivity were independent predictors of the early recurrence.

1. Introduction

Patients with locally advanced rectal cancer (LARC) are treated with neoadjuvant chemoradiotherapy (CRT) prior to total mesorectal excision (TME) to increase the likelihood of inducing tumor regression, achieve a negative margin, and reduce the risk of local recurrence. Postoperative adjuvant chemotherapy is also recommended to reduce the risk of distant metastasis. These treatments not only maintain high levels of local tumor control but also result in long-term survival.[1,2]

Nevertheless, recurrence after perioperative CRT and curative surgery has been reported to be between 25% and 40% in LARC, depending on the progression of the initial pathological stage of the disease and difference in follow-up period.[3,4] In particular, distant metastasis is the most common cause of death in LARC patients.[5] The lung is the most common organ for metastasis in rectal cancer, followed by the liver.[6] Early recurrences within 1 year after surgery for primary rectal cancer have been linked to poor survival.[3,7] These may exist as micrometastatic foci at the time of initial diagnosis.[8]

Early recurrence after completion of scheduled treatment is extremely discouraging for patients and their family members as this indicates that the cancer may be too difficult to treat. As mentioned earlier, a short interval to disease progression may reflect aggressive biological behavior and poor oncological outcomes.

In this situation, the current standard guidelines for the treatment of LARC are revisited. Patients with poor response after completion of preoperative CRT usually undergo surgery once an

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objective clinical assessment of tumor response has been made.

This study aimed to investigate the risk factors and prognostic factors associated with early recurrence in LARC patients who received preoperative chemoradiotherapy (pCRT) in combination with TME.

2. Methods

Between January 2010 and December 2016, 714 LARC patients who underwent curative resection after preoperative CRT at our institution were reviewed. Patients with distant metastasis at initial diagnosis or at the work-up stage after preoperative CRT were excluded. Patients who did not undergo preoperative CRT were also excluded. Among the patients included in the study, there were 139 recurrences, which accounted for 19.5%. Among them, the group with recurrence within 1 year after surgery, defined as early recurrence, included 49 patients (early recurrence group). In the remaining 90 patients, recurrence occurred 1 year or more after surgery, and this was defined as late recurrence (late recurrence group). This study was retrospective in design and received approval from our internal review board at Severance Hospital (IRB No. 4-2019-1080).

In the case of neoadjuvant chemoradiotherapy in our institution, among patients with rectal cancer, T3 or T4 stage disease or clinically positive metastatic lymph node was selected after review of imaging study by multidisciplinary tumor board. The total dose of RT was 50.4 Gy in 28 fractions, and capecitabine was given at an oral dosage of 825 mg/m2 bid on each day of the radiotherapy period with the first daily dose applied 2 h before irradiation. About 6 weeks after the completion of neoadjuvant chemoradiotherapy, the response was evaluated, and TME was administered 1–2 weeks later.

In our institution, all LARC patients visited outpatients at least 4 times a year for 2 years after surgery, followed by 2 times a year between 2 and 5 years after surgery. We have been following outpatient follow-up for 5 years unless there is a special event. The same method was applied to the 714 patients in this study and only those with at least one year of outpatient follow-up were included.

Statistical analyses were performed using IBM SPSS Statistics ver. 25.0 (IBM Corp., Armonk, NY, USA). Differences between the groups were tested with chi-squared tests. Overall survival was estimated using the Kaplan-Meier method, and univariate analyses of the significance of prognostic factors were evaluated using the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox regression models. Multivariate analysis of factors associated with recurrence rate was performed using the Cox proportional hazards model with the backward stepwise (likelihood ratio) method. Variables with P values < 0.05 on the univariate analysis were included in the final multivariable model. A P value ≤ 0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

The characteristics of 139 patients with LARC recurrence are summarized in Table 1. Patients with early recurrence (n = 49) were compared with patients with late recurrence (n = 90). Age, sex, body mass index, preoperative carcinoembryonic antigen level, tumor location, sphincter preservation, pre-treatment mrT classification and mrN status, circumferential resection margin (CRM) status, extramural vascular invasion (EMVI) status, and adjuvant chemotherapy were not different between the two groups.

Table 1
Baseline characteristics.

Variables	Recurrence		
	Early	Late	*P*
	(≦12 months, n = 49)	(>12 months, n = 90)	
Age (years)			0.778
<60	26 (53.1%)	50 (55.6%)	
≥60	23 (46.9%)	40 (44.4%)	
Gender, n (%)			0.940
Male	34 (69.4%)	63 (70.0%)	
Female	15 (30.6%)	27 (30.0%)	
BMI (kg/m2) ≥25	15 (30.6%)	18 (20.0%)	0.160
preCEA (ng/mL) ≥5	21 (42.9%)	44 (48.9%)	0.496
Sphincter preservation			0.134
No	0 (0.0%)	4 (4.4%)	
Yes	49 (100.0%)	86 (95.6%)	
Distance from AV (cm)			0.327
Low	16 (32.7%)	37 (41.1%)	
Mid/Upper	33 (67.3%)	53 (58.9%)	
mrT stage ≧ T3	21 (42.9%)	46 (51.1%)	0.352
mrN (+)	39 (79.6%)	73 (81.1%)	0.829
mrCRM (+)	23 (46.9%)	39 (43.3%)	0.683
mrEMVI(+)	16 (32.7%)	37 (41.1%)	0.327
Adjuvant CTx.	42 (85.7%)	82 (91.1%)	0.327

BMI: body mass index, preCEA: preoperative carcinoembryonic antigen, AV: Anal verge, scular invasion, mrCRM: MRI circumferential resection margin, mrEMVI: MRI extramural vascular invasion, CTx: chemotherapy.

3.2. Pathological outcomes

Table 2 shows the pathological outcomes between the early and late recurrence groups. In both groups, well or moderate differentiation was most common, but this was not a statistically significant difference. In terms of tumor regression grade, 39 patients (79.6%) had a poor response in the early recurrence group compared with 74.4% in the late recurrence group, but this difference was not statistically significant. Perineural invasion and lymphovascular invasion were not significantly different between the two groups.

3.3. Patterns of recurrence

Recurrence of rectal cancer can be divided into local recurrence and systemic recurrence. Local recurrence occurred in 11.1% of the late recurrence group but not in the early recurrence group. The occurrence of systemic recurrence was not significantly different in the two groups, but local and systemic recurrences were much higher in the early recurrence group than in the late recurrence group. In the early recurrence group, all 49 patients showed a systemic recurrence pattern. The results are shown in Table 3.

3.4. Site of systemic recurrence

Table 4 compares the sites of systemic recurrence in both groups. Lung metastasis was the most common in both groups, followed by liver metastasis. Transition to the peritoneum, brain, and bone tended to be about twice as likely in the early recurrence group than that in the late recurrence group.

3.5. Factors associated with early recurrence

In the univariate analysis, the risk factors for early recurrence were lymphovascular invasion, perineural invasion, clinical EMVI, ypT stage 3 or more and n stage positive, pathological CRM positive, and tumor regression grade 3 or more. Multivariate analysis was performed with the univariate analysis factors and a P-value threshold of ≤0.05. A positive ypN stage (HR 2.110, CI 1.144–3.892,

Table 2
Pathologic outcomes.

Variables	Recurrence		
	Early (<12 months, n = 49)	Late (≧12 months, n = 90)	*P*
Differentiation			0.665
WD/MD	46 (93.9%)	87 (96.7%)	
PD/Mucinous	3 (6.1%)	3 (3.3%)	
Tumor regression grade			0.496
TRG 1-2	10 (20.4%)	23 (25.6%)	
TRG 3-5	39 (79.6%)	67 (74.4%)	
ypT stage			0.456
pCR-2	16 (32.7%)	24 (26.7%)	
T3-4	33 (67.3%)	66 (73.3%)	
ypN stage			0.192
N0	28 (57.1%)	41 (45.6%)	
N1-2	21 (42.9%)	49 (54.4%)	
CRM (≤1.0 mm)	8 (16.3%)	10 (11.1%)	0.382
Margin involvement	1 (2.1%)	0 (0.0%)	0.353
Perineural invasion	5 (10.2%)	11 (12.2%)	0.722
Lymphovascular invasion	9 (18.4%)	13 (14.4%)	0.545

WD: well differentiated, MD: moderately differentiated, PD: poorly differentiated, pCR: pathological complete response, CRM: circumferential resection margin.

Table 3
Patterns of recurrence.

Patterns	Recurrence		
	Early (<12 months, n = 49)	Late (≧12 months, n = 90)	*P = 0.013*
Local only	0 (0%)	10 (11.1%)	
Local + Systemic	16 (32.7%)	18 (20.0%)	
Systemic only	33 (67.3%)	62 (68.9%)	

Table 4
Site of systemic recurrence.

Recurrence site	Recurrence	
	Early (<12 months)	Late (≧12 months)
Liver	18 (37.5%)	29 (31.9%)
Lung	29 (60.4%)	51 (56.0%)
Extra-abdominal LN	1 (2.1%)	1 (1.1%)
Intra-abdominal LN	3 (6.3%)	3 (3.3%)
Peritoneum	3 (6.3%)	2 (2.2%)
Brain	4 (8.3%)	2 (2.2%)
Adrenal	1 (2.1%)	2 (2.2%)
Pancreas	0 (0.0%)	1 (1.1%)
Bone	3 (6.3%)	3 (3.3%)

P = 0.017) and tumor regression grade of 3 or more (HR 2.962, CI 1.434–6.119, P = 0.003) showed statistically significant results. The results are shown in Table 5.

3.6. Overall survival per recurrence group

A Kaplan-Meier curve comparing overall survival in the early and late recurrence groups is shown in Fig. 1. Although the P-value was 0.121 and no significant results were obtained, the overall survival at 3 years after surgery was 76.8% in the early recurrence group and 90.8% in the late recurrence group.

4. Discussion

In this study, we did not find any difference in the baseline characteristics or pathological outcomes in patients in the early and late recurrence groups. However, all patients in the early recurrence group showed a systemic recurrence pattern, which was observed a higher rate than that in the patients in the late recurrence group.

Despite significant advances in the management of LARC, recurrence still occurs. With the advancement of surgical technology, radiotherapy to reduce the possibility of local recurrence and preoperative chemotherapy have resulted in much lower recurrence rates in recent years. In spite of this, recurrence remains a highly morbid, debilitating condition. Past studies have reported recurrence rates of up to 40% after curative treatment for rectal cancer.[9,10] However, the recently introduced National Comprehensive Cancer Network guidelines reported a recurrence rate of 20.8%, which is similar to the recurrence rate of 20.0% in our LARC patients.[6] This recurrence rate is still high, and notable efforts are being made to lower it.

Many studies reported that systemic recurrence has a poorer prognosis than local recurrence in patients with rectal cancer after curative resection.[11–13] In this study, although no statistically significant difference was found between the two groups, the 3-year overall survival rate of 76.8% in the early recurrence group was somewhat lower than that of 90.8% in the late recurrence group. This may be attributed to the earlier onset of recurrence, but it also disproves the more systemic recurrence pattern in the early recurrence group. Because the number of patients in this study was not sufficiently large, it is believed that the survival rate does not show statistically significant results. However, since the tendency was confirmed in this study, a meaningful result will be obtained if more patients are analyzed in the future or supplemented with multicenter studies.

In this study, we identified that the lung was the most common systemic recurrence site in both early and late recurrence groups of LARC patients. Unlike the liver, which is generally known to be the distant metastasis site of colorectal cancer, all patients included in this study had rectal cancer, and lymphatic fluid drains directly to the lung through the lateral pathway.[14,15] In addition, the distant metastasis of rectal cancer, which shows a higher proportion of lung metastasis than liver metastasis, can be explained as hematogeneous metastasis by bypassing the liver via direct venous drainage into the vena cava.[16–18]

Early recurrence can be divided into two categories: the first includes cases without metastasis at the time of diagnosis and

Table 5
Uni- and multivariate analysis of risk factors associated with early recurrence using cox regression model.

Factors	Early Recurrence			
	Univariate	Multivariate		
	P	HR	95% CI	*P*
Age (<60 vs. ≥60 years)	0.886			
Gender (male vs. female)	0.556			
BMI (<25 vs. ≥25 kg/m2)	0.376			
preCEA (<5 vs. ≥5 ng/mL)	0.071			
LVI	0.004			
PNI	0.035			
mrT stage ≧ T3c	0.166			
mrN (+)	0.683			
mrEMVI	0.046			
mrCRM	0.655			
Resection margin (+)	0.236			
Histology (WD/MD vs. PD/Mucinous)	0.655			
ypT stage (T0-2 vs. T3-4)	0.002			
ypN stage (N0 vs. N1-2)	0.002	2.110	1.144–3.892	0.017
Pathologic CRM (+)	0.003			
TRG (12 vs. 345)	0.001	2.962	1.434–6.119	0.003
Adjuvant CTx (Yes vs. No)	0.694			

BMI: body mass index, preCEA: preoperative carcinoembryonic antigen, LVI: lymphovascular invasion, PNI: perineural invasion, cEMVI: clinical extramural vascular invasion, cCRM: clinical circumferential resection margin. WD: well differentiated, MD: moderately differentiated, PD: poorly differentiated, pTNM: AJCC pathologic staging 7th edition,TRG: Mandard tumor regression grade, HR: hazard ratio, 95% CI: 95% confidence interval.

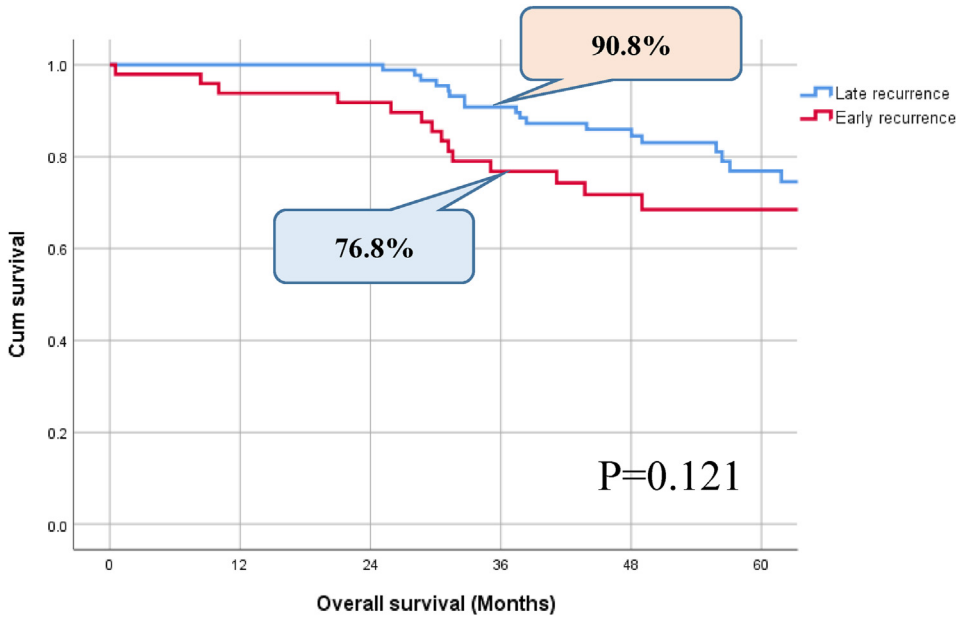

Fig. 1. KM analysis for overall survival per recurrence group.

surgery, and the second includes cases where metastasis has already been detected at the time of diagnosis. However, given the small size of the metastasis, it is not detected on abdominopelvic and chest computed tomography, magnetic resonance imaging, and even positron emission tomography-computed tomography during work-up.[8] In the future, when the development of diagnostic methods enables the examination of metastatic lesions smaller than the current smallest size that can be evaluated, metastasis can be confirmed at the time of diagnosis and other treatments can be performed. However, the current treatment is not sufficient for patients in the early recurrence group in whom metastasis is found within 12 months after surgery.

Since the 1990s, fluorouracil plus leucovorin as a neoadjuvant chemoradiation therapy and preoperative radiation therapy with a total dose of 5040 cGy have had a significant effect on improving local control and survival in LARC patients. It is considered a gold standard and has been around for almost 30 years.[19,20] The purpose of neoadjuvant long-course chemoradiation is to enable R0 resection with tumor shrinkage. Although local control has been improved because of these treatments, it is necessary to obtain better results by changing to a more effective schedule of preoperative treatment. Treatment of rectal cancer over the past 30 years has gradually lowered local recurrence rates owing to better imaging of localized and systemic diseases and improved surgical techniques. There has also been development of radiation techniques and chemotherapy regimens. In addition, non-surgical

treatment in patients with a complete clinical response after pCRT has been routinely accepted in patients requiring abdominoperineal resection. These changes led to the development of a treatment called total neoadjuvant therapy, wherein the treatment which is usually administered as postoperative (adjuvant) chemotherapy is shifted to the preoperative setting.[21,22] Despite our wide understanding of biology and accurate imaging for rectal cancer, a variable range of treatment outcomes remains; hence, we need to plan more tailored treatment strategies based on the patient's subcategory.

Recently, consolidation chemotherapy after short-course radiotherapy has been introduced as a treatment method. According to Bojko et al, patients received preoperative 5 × 5 Gy irradiation over 5 days with consolidation chemotherapy consisting of three cycles of FOLFOX4. The short-term outcome was better, acute toxicity was lower, and no difference was found in postoperative complications compared with conventional treatment.[23] The RAPIDO trial was similar, but the chemotherapy administered was slightly different, wherein short-course radiotherapy (5 Gy × 5) was followed by full-dose chemotherapy (capecitabine and oxaliplatin) over six cycles before surgery.[24,25]

In this study, we did not find any risk factors present at the time of diagnosis that were associated with the possibility of early recurrence. Pathological low tumor regression grade and ypN stage positivity were found to be independent risk factors in the early recurrence group compared with the non-recurrence group. There is no way to determine the risk factors for early recurrence at diagnosis or before surgery. Moreover, pathological low tumor regression grade and ypN stage positivity are present after surgery; thus, frequent and close follow-up with adjuvant chemotherapy is necessary to determine recurrence within 1 year after surgery. Further research is needed to identify risk factors that can predict early recurrence after diagnosis and before neoadjuvant treatment begins.

This study had several limitations. First, this study was a retrospective analysis of a single institution in Korea, and all patients were Asian, reducing the generalizability of our results. On the other hand, almost all patients received postoperative follow-up at our hospital, which is a major advantage. Second, we still have not found a factor that predicts early recurrence at the time of diagnosis. If we could predict recurrence at the time of diagnosis, this might improve the survival rate, as we could attempt different treatments.

Our findings may contribute to a more prolonged disease-free interval for these patients. First, we must identify patients who are at risk of early recurrence before starting treatment or restaging after neoadjuvant chemoradiation. Then, current standard treatment schedules may be changed in sequence in this high-risk group of patients.

In conclusion, in LARC patients who received pCRT followed by TME, tumor regression grade and ypN stage positivity were independent predictors of early recurrence. Although early recurrence was not predictable before pCRT, poor responders (low tumor regression grade) and those with ypN stage positivity need more careful monitoring owing to the possibility of early recurrence. Conventional neoadjuvant chemoradiation may not be enough to treat patients with this early recurrence pattern. Therefore, different treatments such as total neoadjuvant treatment and consolidation chemotherapy are necessary, and further research is needed to develop alternative treatment methods.

All authors made substantial contributions to conception, design, acquisition of data, analysis and interpretation of data, and drafting the article and revising it critically for important intellectual content and gave final approval of the version to be published.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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