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Retrospective Study

Predictive factors for early distant metastasis after neoadjuvant chemoradiotherapy in locally advanced rectal cancer

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Abstract

BACKGROUND

Distant relapse is the leading cause of cancer-related death in locally advanced rectal cancer. Neoadjuvant chemoradiation (NACRT) followed by surgery inevitably delays delivery of systemic treatment. Some patients show early distant metastasis before systemic treatment.

AIM

To identify the most effective treatments. We investigated prognostic factors for distant metastasis, especially early distant metastasis, using the standard treatment paradigm to identify the most effective treatments according to recurrence risk.

METHODS

From January 2015 through December 2019, rectal cancer patients who underwent NACRT for having clinical T 3-4 or clinical N 1-2 disease according to the 8th American Joint Committee on Cancer staging system were included. Radiotherapy was delivered to the whole pelvis with concomitant chemotherapy. Patients received surgery 6-8 wk after completion of NACRT. Adjuvant chemotherapy was administered at the physician's discretion.

RESULTS

A total of 127 patients received NACRT. Ninety-three patients (73.2%) underwent surgery. The R0 resection rate was 89.2% in all patients. Pathologic tumor and node downstaging rates were 41.9% and 76.3%. Half the patients ($n = 69$) received adjuvant chemotherapy after surgery. The 3-year distant metastasis-free survival (DMFS) and overall survival (OS) rates were 81.7% and 83.5%. On univariate analyses, poorly differentiated tumors, > 5 cm, involvement of mesorectal fascia (MRF), or presence of extramural involvement (EMVI) were associated with worse DMFS and OS. Five patients showed distant metastasis at their first evaluation after NACRT. Patients with early distant metastasis were more likely

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to have poorly differentiated tumor ($P = 0.025$), tumors with involved MRF ($P = 0.002$), and EMVI ($P = 0.012$) than those who did not.

CONCLUSION

EMVI, the involvement of MRF, and poor histologic grade were associated with early distant metastasis. In order to control distant metastasis and improve treatment outcome, selective use of neoadjuvant treatment according to individualized risk factors is necessary. Future studies are required to determine effective treatment strategies for patients at high risk for distant metastasis.

Key Words: Rectal cancer; Neoadjuvant chemoradiotherapy; Distant metastasis; Extramural venous invasion

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Core Tip: This is a retrospective study to investigate prognostic factors for distant metastasis, especially early distant metastasis, using the standard treatment paradigm to identify the most effective treatments according to recurrence risk. Poorly differentiated tumors, involvement of mesorectal fascia, or presence of extramural involvement were associated with distant metastasis and early distant metastasis. For patients with these risk factors, early systemic chemotherapy could be beneficial. Selective use of neoadjuvant treatment other than the current standard treatment according to individualized risk factors is necessary.

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INTRODUCTION

The management of locally advanced rectal cancer has improved in recent decades. Surgery quality and approach have improved, and pelvic radiotherapy and chemotherapy have been incorporated into standard treatments. Management of locally advanced rectal cancer, however, remains challenging in most cases. Before pelvic radiotherapy, local recurrence was a common pattern of treatment failure. Along with total mesorectal excision (TME), neoadjuvant chemoradiation (NACRT) has decreased the local recurrence (LR) rate from 35% to less than 10%^[1]. Although NACRT has contributed to decreased local recurrence, distant relapse rates have not changed, and remain at approximately 30% in locally advanced rectal cancer. Currently, distant relapse is the leading cause of cancer-related death in rectal cancer patients^[2].

Adjuvant chemotherapy has been recommended as a systemic treatment in patients with locally advanced rectal cancer treated with NACRT and surgery, but its efficacy remains controversial due to poor compliance and unclear survival benefit^[2]. Another problem is that some patients show early distant metastasis before systemic treatment. NACRT followed by surgery, which is the current standard treatment for patients with locally advanced rectal cancer, inevitably delays delivery of systemic treatment. Early systemic treatments prior to surgery have been proposed to improve systemic control. Several randomized trials and observational studies have integrated systemic chemotherapy into neoadjuvant treatment to overcome systemic treatment delay, thereby reducing distant relapse and increasing treatment compliance^[2]. Some studies have incorporated chemotherapy prior to NACRT while others omitted radiotherapy from neoadjuvant treatment paradigms^[3-24].

The treatment sequence for multimodality treatment should be individualized according to patient age, comorbidities, stage, and tumor characteristics. Prognostic factors for distant metastasis and patient characteristics, such as eligibility, were different across studies. Therefore, we investigated prognostic factors for distant

metastasis, especially early distant metastasis, using the standard treatment paradigm to identify the most effective treatments according to recurrence risk.

MATERIALS AND METHODS

Patients and initial evaluations

This study was approved by the Institutional Review Board of Dankook University Hospital (DKUH 2020-08-26). The authors retrieved data from 148 consecutive rectal cancer patients from January 2015 through December 2019 who underwent NACRT for clinical T (cT) 3-4 or clinical N (cN) 1-2 disease according to the 8th American Joint Committee on Cancer staging system. Patients with resectable metastatic disease were included because aggressive local treatment and metastasectomy can be curative. Patients were excluded if they did not complete NACRT, had no imaging evaluation after NACRT, had multiple malignant tumors or had unresectable metastatic disease. Pretreatment evaluations for diagnostic confirmation and clinical stage assignment included a complete history and physical examination, complete blood counts, blood chemistry profiles, carcinoembryonic antigen, colonoscopy with biopsy, and computed tomography (CT) of the chest and abdomen/pelvis. Magnetic resonance imaging (MRI) of the rectum was performed in 91 patients (71.1%), and whole-body 18F-fluorodeoxyglucose positron emission tomography with CT was performed in 90 patients (70.3%). Size and shape criteria for diagnosing lymph-node metastasis were as follows^[25]: Short-axis length ≥ 5 mm; if short-axis length < 5 mm, additional criteria, such as round shape, heterogeneity of appearance, irregular border, presence of mucin and/or calcifications, or loss of the normal fatty hilum, were evaluated.

Treatment

All patients underwent CT scans with a belly board before setting a radiotherapy plan. Among all patients, 117 (92.1%) were treated with 3-dimensional conformal radiotherapy (3D-CRT) and 10 (10.0%) were treated with intensity-modulated radiotherapy. Radiotherapy was delivered to the whole pelvis at a dose of 45 Gy with 1.8 Gy *per* fraction for five weeks, five days *per* week. The boost dose was delivered to the gross tumor at a dose of 5.4 Gy with 1.8 Gy *per* fraction. During the radiotherapy course, concomitant chemotherapy was given as capecitabine 825 mg/m² twice daily on radiotherapy days. Patients were assessed weekly for toxicity during CRT. Patients received surgery 6-8 wk after completion of NACRT. Adjuvant chemotherapy was administered at the physician's discretion. Adjuvant chemotherapy commenced 6-8 wk after surgery.

Surveillance and statistical analyses

The first follow-up evaluations included physical examination, blood tests, colonoscopy with or without biopsy, and abdominopelvic CT or MRI of the rectum 6-8 wk after NACRT completion. After the planned treatment, regular follow-up evaluations were scheduled at 3 mo intervals for the first 2 years and then at 6 mo intervals thereafter. LR recurrence was defined as relapse within the RT target volume or regional lymphatics. Distant metastasis was defined as relapse other than LR recurrence including peritoneal seeding and hematogenous metastasis. Survival durations was calculated from the date of treatment until the date of event (death or relapse) or the date of the latest follow-up. The rates of overall survival (OS), locoregional control (LRC), distant metastasis-free survival (DMFS), and disease-free survival (DFS) were calculated using the Kaplan-Meier method, and comparisons between subgroups were performed using the log-rank test. Cox proportional hazard regression analysis was used to determine the independent prognostic factors. For group comparisons, categorical variables were compared using the chi-square test or Fisher's exact test. Continuous variables were compared using the t-test or the Mann-Whitney test. All *P* values were two-sided, and *P* < 0.05 were considered statistically significant throughout the study. Statistical analyses were performed using SPSS software, standard version 26.0 (IBM Corporation, Armonk, NY, United States).

RESULTS

Patient characteristics

A total of 127 patients received NACRT from 2015 to 2019 (Table 1). The median age of all patients was 65 (27-92) years. Three patients (2.4%) had poorly differentiated tumors. Most patients had cT3, cT4, or positive lymph nodes. Patients with cT3 disease were divided into the following subcategories: cT3a ($n = 22$), cT3b ($n = 24$), cT3c ($n = 21$), and cT3d ($n = 27$). Nine patients (7.1%) showed mesorectal fascia (MRF) involvement. MRI of the rectum was used, to evaluate the presence of extramural venous invasion (EMVI), and 41 patients (32.3%) showed EMVI. Seven patients had metastatic disease at diagnosis. Thirty-four patients (26.8%) did not undergo surgery for the following reasons: Endoscopic complete remission (CR) after NACRT ($n = 12$), refused surgery ($n = 17$), unfit for surgery due to poor performance status or underlying medical disease ($n = 2$), progressive disease after NACRT ($n = 2$), or expectation of incomplete resection ($n = 1$). Among the 17 patients who refused surgery, nine had tumors within 5 cm from the anal verge or were expected to have an abdominoperineal resection. Five patients refused surgery because of their old age, and three patients refused surgery for other personal reasons. Ninety-three patients underwent surgery: 80 received a scheduled surgery and the remaining 13 received delayed surgery due to refusal ($n = 4$), disease progression ($n = 2$), disease progression after endoscopic CR ($n = 5$), and upfront chemotherapy because of metastatic disease at the first diagnosis. Half the patients ($n = 69$) received adjuvant chemotherapy after surgery. The most common regimen was FOLFOX ($n = 35$), followed by 5-fluorouracil with leucovorin ($n = 18$) and capecitabine ($n = 16$). The compliance rate was 84.1% ($n = 58$). Ten patients could not complete treatment or received a reduced dose.

Treatment outcomes and prognostic factors

After NACRT, 124 patients (97.7%) showed a clinical response in image evaluation. Among the 123 patients who received colonoscopy after NACRT, 61 showed chronic inflammation, ulceration, or no tumor on colonoscopic biopsy. The median interval between the last day of NACRT and surgery was 10.2 wk (range: 1.9-96.1 wk) for all patients and 10 wk (range: 1.9-17.7 wk) for patients who received scheduled surgery. The R0 resection rate was 89.2% in all patients and 90.2% in patients who received scheduled surgery. Pathologic tumor and node downstaging rates were 41.9% and 76.3% in all patients, and 42.7% and 76.8% in patients who received scheduled surgery, respectively (Table 2). Three patients showed CR after surgery.

During the median follow-up duration of 21 mo (range: 3-58.5 mo), 9 patients (7.1%) showed LR, 16 patients (12.6%) showed distant metastasis, and 9 patients (7.1%) died. The LRC, DMFS, DFS and OS rates at 3 years were 90.1%, 81.7%, 75.8%, and 83.5%, respectively. On univariate analyses, poorly differentiated tumors [hazard ratio (HR) = 10.312, $P = 0.044$], tumors > 5 cm (HR = 4.173, $P = 0.033$), and MRF involvement (HR = 11.428, $P = 0.023$) were associated with worse LRC (Table 3). Poorly differentiated tumors, > 5 cm, involvement of MRF, cT3c or d, or presence of EMVI were associated with worse DMFS, DFS, and OS.

Predictive factors for early distant metastasis

Five patients showed distant metastasis at their first evaluation after NACRT: Two patients received chemotherapy followed by surgery, one patient received scheduled surgery due to obstructive symptoms, and two patients received chemotherapy only. Patients with early distant metastasis were more likely to have a poorly differentiated tumor ($P = 0.025$) and a proximally located tumor ($P = 0.031$) than those who did not (Table 4). The proportion of patients with tumors with involved MRF ($P = 0.002$) and EMVI ($P = 0.012$) was higher in patients with early distant metastasis.

DISCUSSION

A multimodality treatment that comprises NACRT followed by TME and adjuvant fluoropyrimidine-based chemotherapy is recommended as a standard treatment for patients with locally advanced rectal cancer^[20]. NACRT has led to significant improvements in the local control of locally advanced rectal cancer^[26]. In contrast, control of distant relapse has not changed and is part of the predominant pattern of treatment failure in locally advanced rectal cancer cases receiving the current standard treatment paradigm^[2]. Although adjuvant chemotherapy is given as a systemic treatment after surgery, compliance with adjuvant chemotherapy has been poor.

Table 1 Baseline patients' characteristics, *n* (%)

Characteristics	Total (<i>n</i> = 127)
Age (yr)	
Median (range)	65 (27-92)
Gender	
Male	93 (73.2)
Female	34 (26.8)
Performance status	
0	99 (78.0)
1	25 (19.7)
2	3 (2.4)
Grade	
Well differentiated	46 (36.2)
Moderately differentiated	78 (61.4)
Poorly differentiated	3 (2.4)
Tumor location	
Distal (10-15 cm from AV)	44 (34.6)
Mid (5-10 cm from AV)	48 (37.8)
Proximal (0-5 cm from AV)	35 (27.6)
Mesorectal fascia involvement	
No	118 (92.9)
Yes	9 (7.1)
Extramural venous invasion	
No	50 (39.4)
Yes	41 (32.3)
Unknown ¹	36 (28.3)
AJCC 8 th T stage	
cT1	0
cT2	17 (13.4)
cT3	94 (74.0)
cT4	16 (12.6)
AJCC 8 th N stage	
cN0	7 (5.5)
cN+	120 (94.5)
AJCC 8 th M stage	
cM0	120 (94.5)
cM1	7 (5.5)
AJCC 8 th stage	
cI	0
cII	7 (5.5)
cIII	113 (89.0)
cIV	7 (5.5)
Surgery	

No	34 (26.8)
Local excision	3 (2.4)
Low anterior resection	77 (60.6)
Abdominoperineal resection	13 (10.2)
Adjuvant chemotherapy	
No	58 (45.7)
Yes	69 (54.3)

¹Patients who did not take magnetic resonance image of the rectum.

AV: Anal verge; AJCC: American Joint Committee on Cancer.

Table 2 Summary of treatment response

Clinical T stage	Pathologic T stage					
	ypT0	ypTis	ypT1	ypT2	ypT3	ypT4
Scheduled surgery						
cT2	2	0	1	6	4	0
cT3	0	1	2	16	35	4
cT4	0	0	0	1	10	0
Unscheduled surgery						
cT2	0	0	0	0	1	0
cT3	1	0	0	3	3	1
cT4	0	0	0	0	0	2

cT: Clinical T.

Approximately half of patients who are eligible for adjuvant chemotherapy initiate treatment after a significant delay or do not receive planned chemotherapy^[26,27]. The long-term treatment outcomes from these strategies have been disappointing, thus, a more effective systemic treatment is required^[2,20].

Historically, lymph node metastasis and \geq T3 were known histopathological risk factors for distant metastasis^[8]. Along with advancements in imaging techniques, locally advanced rectal cancers can be subdivided based on histopathological features, including depth of spread or vascular invasion. The involvements of MRF and EMVI has been shown to be an important prognostic factor, associated with a higher rate of distant metastasis and poorer survival^[5,8,24]. Similarly, the current study showed that involvement of MRF, EMVI, tumor size, and tumor grade were associated with distant metastasis. In the current study, among these factors, MRF, EMVI and tumor grade were associated with early distant metastasis, which occurred during the interval between completion of NACRT and surgery. Early distant metastasis is associated with poor survival^[28]. Therefore, patients with these risk factors should be treated with more aggressive treatment before surgery. These findings suggest that not all rectal cancer patients need NACRT before surgery, and a more individualized treatment approach should be taken that is tailored to the patient's risk factors at baseline. This individualized approach to treatment could lead to excellent oncological outcomes.

Several studies have suggested that early full-dose chemotherapy should be incorporated into neoadjuvant treatment (Tables 5 and 6). The inclusion criteria varied widely between the studies and most studies, and most studies included \geq T3, lymph node metastasis, the involvement of MRF, or EMVI. Early distant metastasis may be present in the form of micrometastatic foci at the time of initial diagnosis^[28]. The disadvantage of NACRT is that systemic chemotherapy is delayed, which may allow the spread and growth of distant micrometastases that may already exist. Early systemic chemotherapy may benefit patients who have a high potential for early distant metastasis, treat such micrometastatic disease and potentially reduce the distant relapse rate^[1]. Another advantage of early chemotherapy is the delivery of an

Table 3 Pretreatment prognostic factors by univariate analysis

Characteristics	n	LRC		DMFS		DFS		OS	
		Hazard ratio (95%CI)	P value	Hazard ratio (95%CI)	P value	Hazard ratio (95%CI)	P value	Hazard ratio (95%CI)	P value
Grade									
Well differentiated	46	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Moderately differentiated	78	1.202 (0.300-4.810)	0.795	2.175 (0.606-7.806)	0.233	1.799(0.653-4.956)	0.256	4.066 (0.499-33.148)	0.190
Poorly differentiated	3	10.312 (1.070-99.393)	0.044	37.827 (5.655-243.040)	< 0.001	22.809 (4.130-125.954)	< 0.001	67.489 (3.594-1267.323)	0.005
Tumor location									
Distal	44	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Mid	48	1.785 (0.327-9.746)	0.527	1.439 (0.344-6.023)	0.618	1.817 (0.547-6.039)	0.330	3.244 (0.362-29.048)	0.293
Proximal	35	1.781 (0.297-10.659)	0.504	3.539 (0.936-13.380)	0.063	3.223 (1.009-10.290)	0.048	6.479 (0.755-55.611)	0.088
Tumor size									
≤ 5 cm	105	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
> 5 cm	22	4.173 (1.120-15.551)	0.033	4.224 (1.569-11.372)	0.004	5.909 (2.555-13.670)	< 0.001	4.224 (1.569-11.372)	0.004
MRF involvement									
No	118	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Yes	9	2.860 (0.355-23.016)	0.323	19.532 (4.787-79.695)	< 0.001	16.082 (5.022-51.503)	< 0.001	19.532 (4.787-79.695)	< 0.001
T3 substage									
T3a or b	46	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
T3c or d	48	70.381 (0.053-94343.482)	0.247	5.272 (1.073-25.898)	0.041	7.852 (1.710-36.052)	0.008	5.272 (1.073-25.898)	0.041
EMVI ¹									
No	50	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Yes	41	11.428 (1.402-93.177)	0.023	4.408 (1.488-13.056)	0.007	4.387 (1.843-12.692)	0.001	4.408 (1.488-13.056)	0.007
Superior rectal lymph node		1.253 (0.973-1.614)	0.081	1.102 (0.870-1.395)	0.420	1.208 (1.005-1.451)	0.044	1.102 (0.870-1.395)	0.420

¹Patients who did not take magnetic resonance image of the rectum were excluded.

MRF: Mesorectal fascia; EMVI: Extramural venous invasion; LRC: Locoregional control; DMFS: Distant metastasis-free survival; DFS: Disease-free survival; OS: Overall survival.

effective dose of chemotherapy using an intact vasculature that has not been disrupted by radiotherapy or surgery. Additionally, early chemotherapy induces tumor vascularity due to tumor shrinkage, allowing for improved oxygenation, which may offer improved sensitivity to chemotherapy or radiotherapy^[29]. Early chemotherapy may also increase patient compliance to systemic chemotherapy, which is the primary weakness of adjuvant chemotherapy^[7]. Another benefit is that the time to temporary ostomy reversal is shorter when no adjuvant chemotherapy is planned^[26]. Early systemic chemotherapy, however, delays surgery and reduces radiotherapy efficacy due to the selective survival of radioresistant clones^[7,29].

Among early chemotherapy studies, several studies have reported treatment outcomes of neoadjuvant chemotherapy (NAC) alone followed by surgery (Table 6). Advancements in surgical techniques have led to significant improvements in local control and have made LR a rare event. Additionally, increasing awareness of potential radiotherapy related risks, such as urinary and sexual dysfunction, and intestinal problems, has led physicians to omit radiotherapy^[23]. This treatment strategy also has the benefit of short treatment duration. Several studies showed comparable

Table 4 Predictive factors for early distant metastasis, *n* (%)

Characteristics	Early metastasis		P value
	Yes (<i>n</i> = 5)	No (<i>n</i> = 122)	
Grade			0.025
Well differentiated	3 (60.0)	43 (35.2)	
Moderately differentiated	1 (20.0)	77 (63.1)	
Poorly differentiated	1 (20.0)	2 (1.6)	
Tumor location			0.031
Distal	0	44 (36.1)	
Mid	1 (20.0)	47 (38.5)	
Proximal	4 (80.0)	31 (25.4)	
MRF involvement			0.002
No	2 (40.0)	116 (95.1)	
Yes	3 (60.0)	6 (4.9)	
EMVI ¹			0.012
No	0	50 (58.1)	
Yes	5 (100)	36 (41.9)	

¹Patients who did not take magnetic resonance image of the rectum were excluded.

MRF: Mesorectal fascia; EMVI: Extramural venous invasion.

results to standard treatment, with pathologic CR rates ranging from 6%-27%^[12,17-24]. However, these promising results are not enough to evaluate whether this treatment was effective in reducing distant metastasis. Additionally, omitting radiotherapy should be considered carefully. The advantage of incorporating radiotherapy into neoadjuvant treatment paradigms includes an increased likelihood of R0 resection, reduced risk of tumor seeding, enhanced radiosensitivity due to intact vasculature, and an increased chance of sphincter preservation surgery^[12]. In a Chinese randomized trial, patients who received NAC without radiotherapy showed a lower pathologic CR rate and a higher lymph node metastasis rate than patients who received NAC with radiotherapy^[20]. Further studies are ongoing^[1].

This study has several limitations. The number of patients who received MR imaging was small. MR imaging allows accurate prediction of MRF involvement and EMVI^[30]. However, in another study, approximately 30%-40% of rectal cancer patients had baseline EMVI positivity on MR images, which is similar to the findings of this study^[24]. This suggests that the proportion of underestimated EMVI may not be high. This study also observed lower pathologic CR rates than other studies of NACRT with capecitabine. The low rate of scheduled surgical resection may affect the poor pathologic CR rate. Due to the inherent nature of retrospective data, selection bias is an important consideration. Despite these limitations, an important strength of this study is that it includes a homogenous group of patients.

CONCLUSION

The results of this study showed that EMVI, the involvement of MRF, and poor histologic grade were associated with early distant metastasis. For patients with these risk factors, early systemic chemotherapy could be beneficial. To control distant metastasis and improve treatment outcomes, selective use of neoadjuvant treatment according to individualized risk factors in addition to the current standard treatment is necessary. Future studies that include carefully applied imaging and randomized design are required to determine effective treatment strategies for patients at high risk for distant metastasis. Several clinical trials are ongoing and awaiting results, thus, development of a reliable method to select patients is necessary.

Table 5 Summaries of studies on neoadjuvant chemotherapy followed by chemoradiotherapy

Study	Design	n	Eligibility	NAC regimen	CRT regimen	AC regimen	Response	Compliance	Recurrence	Survival
Chau <i>et al</i> ^[3]	Prospective single-arm	36	cT3N0-2; cT4N0-2	MMC (× 2); PVI 5-FU	RT 54Gy/30Fx's; PVI 5-FU	MMC; PVI 5-FU	27.8% ¹ after NAC; 80.6% ¹ after CRT	NAC 100%; CRT 100%	LR 2 pts; DM 9 pts	1Y-OS 93.5%; 2Y-OS 70.3%
EXPERT ^[4,5]	Phase II single-arm	105	MR defined disease: MRF involved or threatened, cT3 tumor at or below the levators, cT4, cN2, extramural extension ≥ 5 mm	CAPOX (× 4)	RT 54Gy/30Fx's; capecitabine	capecitabine	74% ¹ after NAC; 89% ¹ after CRT	NAC 89%; CRT 91%	LR 6 pts; DM 21 pts	5Y-OS 75.0%
GCR-3 ^[6,7]	Phase II; RCT	54	MR defined disease: Distal edge within 12 cm from AV, lower third cT3, resectable cT4, cT3-4N+, MRF involved or threatened	CAPOX (× 4)	RT 54Gy/27Fx's; CAPOX	-	Downstaging 43.0%; pCR 14.0%	NAC 94.0%; CRT 85.0%	LR 5%; DM 23%	5Y-OS 75.0%
		49		-	RT 54Gy/27Fx's; CAPOX	CAPOX (× 4)	Downstaging 58.0%; pCR 13.0%	CRT 80.0%; AC 57.0%	LR 2%; DM 21%	5Y-OS 78.0%
COPERNICUS ^[8]	Phase II single-arm	60	Inferior margin ≥ 4 cm from AV, superior margin < S1/2 interspace, tumor > 1 mm from MRF, cT3d, cT4, mrT3a-b with either EMV invasion or mesorectal lymph nodes	Oxaliplatin/5-FU (× 4)	RT 25Gy/5Fx's	Oxaliplatin 5-FU (× 8)	T down staging: 73.0% ¹ after NAC; 74.0% after surgery	NAC 75.0%; AC 37.0%	LR 2 pts; DM 6 pts	2Y-PFS 86.2%
CONTRE ^[9]	Prospective single-arm	39	cT3-4N0, cT1-4N+	mFOLFOX6 (× 8)	RT 50.4Gy/28Fx's capecitabine	-	pCR 33.0%	NAC 92.0%	LR 2 pts; DM 6 pts	-
Schou <i>et al</i> ^[10]	Prospective single-arm	84	MR defined disease: MRF involved or threatened, cT3-4 N+	CAPOX (× 2)	RT 54Gy/27Fx's capecitabine	-	T down staging 69% after surgery pCR 23.0%	NAC 88.0%	LR 1% DM 25%	5Y-OS 67.0%
Dueland <i>et al</i> ^[11]	Prospective single-arm	97	cT3 with < 3 mm from MRF, cT4, N+, resectable synchronous metastasis	Nordic FLOX (× 2)	RT 50Gy/25Fx's; CAPOX	-	pCR 17.3%	NAC 91.0%	LR 4 pts; DM 27 pts	5Y-OS 83.0%
Koeberle <i>et al</i> ^[12]	Phase II single-arm	60	cT3-4 with N- or N+	CAPOX (× 1)	RT 45Gy/25Fx's; CAPOX	-	pCR 23.0%	Oxaliplatin 87.0%	-	-
Maréchal <i>et al</i> ^[13]	Phase II RCT	29	cT2-4, cN+	-	RT 45Gy/25Fx's; 5-FU	-	pCR 28%	NAC 96.0%; CRT 98.0%	-	-
		28		mFOLFOX6 (× 2)	RT 45Gy/25Fx's; 5-FU	-	pCR 25%			
EXPERT-C ^[14]	Phase II RCT	81	MR defined disease: Tumor within 1mm of MRF, cT3 tumor at or below the levators, cT4, presence of EMV invasion, extramural extension 5mm	CAPOX (× 4) cetuximab	RT 54Gy/30Fx's; capecitabine/ cetuximab	CAPOX (× 4); cetuximab	64.0% ¹ after NAC; 84.0% ¹ after CRT	NAC 95.0%; CRT 91.0%	LR 1 pt	-
		83		CAPOX (× 4)	RT 54Gy/30Fx's; capecitabine	CAPOX (x4)	54.0% ¹ after NAC; 76.0% ¹ after CRT	NAC 93.0%; CRT 90.0%	LR 2 pts	-
AVACROSS ^[15]	Phase II single-arm	47	Distal edge ≤ 1 cm from AV, cT3N+, resectable cT4, cT3 tumor in lower third, tumor in middle third with ≤ 2 mm from MRF, N+ with ≤ 2 mm from MRF	CAPOX/bevacizumab (× 4)	RT 50Gy/25Fx's; capecitabine/ bevacizumab	CAPOX (x4)	pCR 34.0%	NAC 85.0%; CRT 83.0%	DM 5 pts	-
Eisterer <i>et al</i> ^[16]	Phase II single-arm	25	MR defined disease: cT3 (< 5 mm from MRF), cT4	CAPOX/bevacizumab (× 3)	RT 45Gy/25Fx's capecitabine	-	pCR 25.0%	NAC 79.2% CRT 94.7%	-	-

PRODIGE23 ^[31]	Phase III	231	cT3-4	mFOLFIRINOX (× 6)	RT 50Gy/25Fx's; capecitabine	mFOLFOX6 or capecitabine	pCR 27.8%	-	-	3Y-DFS 75.7%
		230		-			pCR 12%	-	-	3Y-DFS 68.5%

¹Tumor response evaluation by imaging.

NAC: Neoadjuvant chemotherapy; CRT: Chemoradiotherapy; RT: Radiotherapy; AC: Adjuvant chemotherapy; OS: Overall survival; PFS: Progression-free survival; LR: Local recurrence; DM: Distant metastasis; MR: Magnetic resonance; AV: Anal verge; MRF: Mesorectal fascia; EMV: Extramural venous; MMC: Mitomycin C; PVI: Protracted venous infusion; CAPOX: Capecitabine/oxaliplatin; FLOX: Oxaliplatin/5-FU; FOLFIRINOX: Oxaliplatin/5-FU/Irinotecan; pCR: Pathological complete response; RCT: Randomized controlled trial.

Table 6 Summaries of studies on neoadjuvant chemotherapy without radiotherapy

Study	Design	n	Eligibility	NAC regimen	CRT regimen	AC regimen	Response	Compliance	Recurrence	Survival
Koizumi <i>et al</i> ^[17]	Phase II single-arm	30	Lower edge under S2, cT3-4	FOLFOX (× 6)	-	-	pCR 6.7%	NAC 93.3%	LR 2 pts; DM 5 pts	3Y-OS 95.7%
FORTUNE ^[18]	Phase II single-arm	106	cT3-4, cN1-2, distal edge < 12 cm from AV	mFOLFOXIRI (× 4-6)	RT 50.4Gy/28Fx's; mFOLFOX6 ¹ or RT 25Gy/5Fx's	mFOLFOX6(× 6)	pCR 20.4%; pCR 17.4% after NAC	NAC 100%	-	-
Ishii <i>et al</i> ^[19]	Prospective single-arm	26	cT3-4 with cN0-2	IFL (× 2)	-	-	Downstaging 57.0%; pCR 3.8%	NAC 100%	-	5Y-OS 84.0%
FOWARC ^[20, 21]	Phase III RCT	165	cT3-4, N1-2	-	RT 45Gy/25Fx's 5-FU	5-FU (× 7)	pCR 14.0%	CRT 88.4%	LR 8.0%	3Y-OS 91.3%
		165		-	RT 45Gy/25Fx's mFOLFOX6	mFOLFOX (× 7)	pCR 27.5%	CRT 94.9%	LR 7.0%	3Y-OS 89.1%
		165		mFOLFOX6 (× 4-6)	-	mFOLFOX6(× 6-8)	pCR 6.5%	NAC 94.5%	LR 8.3%	3Y-OS 90.7%
Schrag <i>et al</i> ^[22]	Phase II single-arm	32	Distal edge within 5-12cm from AV, cT3N-, cT3N+	mFOLFOX6/bevacizumab (× 6)	RT 50.4Gy/28Fx's 5-FU ¹	FOLFOX	pCR 25.0%	NAC 93.8%	LR 0; DM 12.5%	4Y-OS 91.0%
N-SOG 03 ^[23]	Phase II single-arm	32	MR defined disease: Inferior margin below the S2 lower margin, MRF involved or threatened, cT3b-d, cT4, cN2	CAPOX/bevacizumab (× 4)	-	-	T down staging 54.0% after surgery pCR 25.0%	NAC 79.2%; CRT 94.7%	-	-
GEMCAD 0801 ^[24, 32]	Phase II single-arm	46	MR defined disease: Distal edge > 5 cm from AV, cT3 (≥ 2 mm from MRF)	CAPOX/bevacizumab (× 4)	-	-	pCR 19.5%	NAC 95.6%	LR 2 pts; DM 8 pts; Both 1 pt	-

¹Chemoradiotherapy if any progression after neoadjuvant chemotherapy.

NAC: Neoadjuvant chemotherapy; CRT: Chemoradiotherapy; RT: Radiotherapy; AC: Adjuvant chemotherapy; OS: Overall survival; LR: Local recurrence; DM: Distant metastasis; MR: Magnetic resonance; AV: Anal verge; MRF: Mesorectal fascia; CAPOX: Capecitabine/oxaliplatin; IFL: Irinotecan/fluorouracil/leukovorin; pCR: Pathological complete response; RCT: Randomized controlled trial.

ARTICLE HIGHLIGHTS

Research background

Distant relapse has become the leading cause of cancer death in locally advanced rectal cancer. The standard treatment of locally advanced rectal cancer, neoadjuvant chemoradiation (NACRT) followed by surgery, inevitably delays delivery of systemic treatment.

Research motivation

This study investigated prognostic factors for distant metastasis, especially early distant metastasis, using the standard treatment paradigm to identify the most effective treatments according to recurrence risk.

Research objectives

We investigated prognostic factors for early distant metastasis, using the standard treatment paradigm to identify the most effective neoadjuvant treatments according to recurrence risk.

Research methods

The authors retrieved data from 148 consecutive rectal cancer patients from January 2015 through December 2019 who underwent NACRT for having clinical T 3-4 or clinical N 1-2 disease according to the 8th American Joint Committee on Cancer staging system.

Research results

Patients with early distant metastasis were more likely to have poorly differentiated tumor ($P = 0.025$), tumors with involved mesorectal fascia ($P = 0.002$), and extramural venous invasion ($P = 0.012$) than those who did not. Due to the small number of patients who received magnetic resonance imaging and inherent limitation of retrospective study, prospective studies with large number of patients are needed.

Research conclusions

For patients with risk factors for early distant metastasis, early systemic chemotherapy could be beneficial. According to the risk factors, neoadjuvant treatment should be individualized.

Research perspectives

Future studies that include carefully applied imaging and randomized design are required.

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