Ann Surg Oncol
https://doi.org/10.1245/s10434-018-6828-4

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – COLORECTAL CANCER

C-Reactive Protein Level Predicts Survival Outcomes in Rectal Cancer Patients Undergoing Total Mesorectal Excision After Preoperative Chemoradiation Therapy

Woo Ram Kim, MD[1,2], Yoon Dae Han, MD[2], and Byung Soh Min, MD[2]

[1]Department of Surgery, CHA Bundang Medical Center, CHA University, Seongnam, Gyeonggi, Korea; [2]Department of Surgery, Yonsei University College of Medicine, Yonsei University Health System, Seoul, Korea

ABSTRACT

Background. Systemic inflammatory response, as measured by C-reactive protein (CRP), is associated with prognosis in various types of human malignancies. However, to the best of our knowledge, the clinical significance of CRP in patients with locally advanced rectal cancer that undergo preoperative chemoradiation has not been investigated in detail. This retrospective study validates CRP as a potential predictive marker for survival outcomes in rectal cancer patients.

Methods. In this study, we enrolled 125 patients that received total mesorectal excision after preoperative chemoradiation for rectal cancer between January 2003 and December 2010. We investigated the association between preoperative CRP and clinicopathological characteristics and assessed the prognostic value of CRP.

Results. The median follow-up was 41 months. Elevated CRP showed significant correlation with high histological grade ($P = 0.009$) and cancer recurrence ($P = 0.027$). The 5-year disease-free survival and cancer-specific survival were significantly lower in the elevated CRP group ($P = 0.001$). Moreover, CRP was the strongest predictive factor for cancer-specific survival in multivariate analysis ($P = 0.001$). In the subgroup analysis, elevated CRP was a significant prognostic factor in patients with node-positive disease ($P = 0.025$) and was associated with poorer tumor regression (TRG4–5; $P = 0.011$).

Conclusions. The results of our study suggest that preoperative CRP level shows prognostic significance in rectal cancer patients that have undergone chemoradiation. Therefore, preoperative CRP may help clinicians to identify patients that need additional therapy to reduce systemic failure.

In the past several decades, several studies have shown that inflammation is related not only to carcinogenesis but also to cancer progression.[1,2] Currently, it is widely accepted that tumor growth is promoted by proinflammatory cytokines and chemokines that are released from tumor-infiltrating leukocytes, which are themselves stimulated by the tumor. Therefore, inflammatory markers, such as C-reactive protein (CRP) and interleukin-6 (IL-6), are elevated in various types of human malignancies and are closely related to the prognosis of cancer patients.[3–8]

CRP is an acute phase protein that is synthesized in the hepatocytes and is induced by acute inflammation.[9] Since CRP was first described as a potential prognostic factor of colorectal cancer in 1998, subsequent studies have demonstrated its clinical significance in colorectal cancer.[6,10–16] Toiyama et al. demonstrated that patients with inadequate lymph node retrieval in stage II and III colorectal cancer showed a different clinical course based on CRP levels. Moreover, Fukuchi et al.[17] reported that pretreatment serum CRP levels were associated with the survival outcomes in patients with stage IV colorectal cancer.[13]

Currently, preoperative chemoradiation therapy (pCRT) is accepted as a standard therapy for locally advanced rectal cancer, especially for local tumor control. However, the incidence of systemic failure has remained unchanged, and the overall survival has shown no improvements. Thus, the prediction of cancer recurrence or poor prognosis may enable us to treat patients more aggressively.

© Society of Surgical Oncology 2018

First Received: 14 May 2018

B. S. Min, MD
e-mail: BSMIN@yuhs.ac

Published online: 04 October 2018

To the best of our knowledge, the clinical significance of systemic inflammatory response after chemoradiation in rectal cancer has not been thoroughly elucidated to date. Therefore, this study was designed to elucidate the clinical relevance of CRP levels in rectal cancer patients undergoing pCRT followed by total mesorectal excision (TME).

METHODS

Patients

We reviewed the medical records of consecutive patients that underwent TME after pCRT for the treatment of rectal cancer at a tertiary referral colorectal cancer center between January 2003 and December 2010. The eligible patients were pathologically diagnosed with adenocarcinoma arising from rectum without systemic metastasis and underwent surgical resection with curative intent. Patients who had emergency surgery, inflammatory bowel disease, palliative surgery, and missing data were excluded from the study. Finally, 125 patients were included in this study. The internal reference value of CRP was 0.8 mg/dL, and patients were categorized into two groups: those with normal ($\leq$ 0.8 mg/dL) or elevated ($>$ 0.8 mg/dL) serum CRP level. The serum CRP level was measured at least 4 weeks after the completion of pCRT and within 2 weeks before surgery. The study protocol was reviewed and approved by the Institutional Review Board (IRB 02-2018-0044).

Preoperative Chemoradiation and Surgery

Pretreatment assessments included clinical examination, blood cell count, serum profiles, and serum carcinoembryonic antigen (CEA) levels. Pretreatment tumor staging was performed by chest radiography, chest CT scan, abdominal and pelvic CT scan, and pelvic MRI. Clinical TMN status was evaluated using pelvic MRI in all patients. Positron emission tomography-computed tomography (PET-CT) and transrectal ultrasound (TRUS) were performed if required.

Indications for pCRT included T3, T4, or positive lymph node based on radiological examinations. The pCRT consisted of 5-fluorouracil (5-FU)-based chemotherapy and pelvic irradiation (4500–5040 cGy) in 25 fractions of 180 cGy/day over 5 weeks. Radiation was delivered with a 6 MV/10 MV dual photon linear accelerator using the four-field box technique. The chemotherapy regimen included continuous intravenous infusion of 5-FU at 425 mg/m^2/day and leucovorin at 20 mg/m^2/day during weeks 1 and 5 of radiotherapy or oral administration of Capecitabine at 850 mg/m^2/day twice a day for 5 weeks. Curative resection was performed 6–8 weeks after completion of pCRT. The standard surgical procedure was TME. Adjuvant chemotherapy was applied to all patients within 4–6 weeks after surgery, except in cases in which patients refused additional therapy or demonstrated severe chemotoxicity. Adjuvant chemotherapy regimen included four cycles of fluorouracil and leucovorin (fluorouracil 425 mg/m^2/day and leucovorin 20 mg/m^2/day on days 1–5, every 4 weeks) or five cycles of oral administration of Capecitabine, 1250 mg/m^2/day, two times every 3 weeks.

Tumor Regression Grade

Rectal cancer patients that had undergone pCRT were assessed for five tumor regression grades (TRG1–5), as suggested by Mandard et al.[18] TRG1 (complete regression) was defined as the absence of residual microscopic tumors; TRG2 is the presence of rare residual cancer cells scattered through the fibrosis; TRG3 increased number of residual cancer cells but predominantly fibrosis; TRG4 residual cancer outgrowing fibrosis; and TRG5 absence of regressive changes. We defined patients belonging to TRG1–3 as good tumor responders and patients belonging to TRG4–5 as poor responders.

Statistical Analysis

The association between CRP status and clinicopathologic characteristics was analyzed by using Chi squared tests. Disease-free survival (DFS) and cancer-specific survival (CSS) rate were defined as the proportion of patients that are alive without any evidence of cancer recurrence upon consecutive imaging studies in a specified period, and the proportion of patients who have not died from cancer in a specified period, respectively. DFS and CSS were analyzed using Kaplan–Meier estimate curves, and the differences were examined using log-rank tests. Cox proportional hazard regression test was used to estimate univariate and multivariate hazard ratios for recurrence and prognosis. Multivariate survival analysis was performed using factors that were found to be significant in the univariate survival analysis. Logistic regression analysis was used to identify factors associated with prognosis and recurrence between CRP and TRG. All P values were two-sided, and $P < 0.05$ was considered to be statistically significant. Statistical analysis was performed using the SPSS statistical software (Statistical Product and Service Solution 20.0 for Windows; SPSS Inc., Chicago, IL).

RESULTS

The median follow-up period was 41 (range: 20–61) months. Eighty-six patients with normal CRP and 39 patients with elevated CRP were included in this study. Patients with

normal CRP showed a more favorable histological grade than patients with high CRP. Poor response after pCRT (TRG4–5) was more frequent in the elevated CRP group. Except for differentiation and tumor regression grade (TRG), the remaining anthropometric data and tumor characteristics were similar between the two groups (Table 1).

During the study period, 43 recurrences were recorded (24 recurrences [27.9%] in normal CRP and 19 recurrences [48.7%] in elevated CRP). Cancer-related death occurred in 22 patients (7 [8.1%] in normal CRP and 15 [38.5%] in elevated CRP). Patients with elevated CRP showed significantly poorer 5-year DFS and CSS rates than those with normal CRP (47.5 vs. 69.7%, $P = 0.014$; 48.7 vs. 89.5%, $P = 0.001$, respectively; Fig. 1a, b).

Univariate analyses identified body mass index (BMI), histological grade, ypT, ypN, ypTNM stage, and CRP as significant prognostic factors for DFS. However, multivariate analyses using the Cox proportional hazards model showed that ypN status (hazard ratio [HR] = 2.840, 95% confidence interval [CI]

TABLE 1 Patient demographics of 125 patients who underwent preoperative chemoradiation for rectal cancer

Variables	CRP (mg/dL)		
	≤ 0.8 (*N* = 86)	> 0.8 (*N* = 39)	*P* value
Age (years)			> 0.999
< 65	62 (72.1%)	28 (71.8%)	
≥ 65	24 (27.9%)	11 (28.2%)	
Gender, *n* (%)			> 0.999
Male	59 (68.6%)	27 (69.2%)	
Female	27 (31.4%)	12 (30.8%)	
BMI (kg/m^2)			0.82
< 25	66 (76.7%)	31 (79.5%)	
≥ 25	20 (23.3%)	8 (20.5%)	
Preoperative serum CEA (ng/mL)			0.567
< 5	47 (54.7%)	19 (48.7%)	
≥ 5	39 (45.3%)	20 (51.3%)	
Tumor size (cm), mean ± SD	2.12 ± 1.70	2.54 ± 1.97	0.226
Differentiation			0.009
Well + moderate	81 (97.6%)	30 (83.3%)	
Poor + mucinous	2 (2.4%)	6 (16.7%)	
Tumor regression grade (TRG)	(*N* = 84)	(*N* = 34)	0.011
1	19 (22.6%)	5 (14.7%)	
2	25 (29.8%)	7 (20.6%)	
3	30 (35.7%)	10 (29.4%)	
4	9 (10.7%)	9 (26.5%)	
5	1 (1.2%)	3 (8.8%)	
Distance from anal verge (cm)			0.356
AV < 5 cm	36 (41.9%)	21 (53.8%)	
AV 5–10 cm	44 (51.2%)	15 (38.5%)	
AV > 10 cm	6 (7.0%)	3 (7.7%)	
ypT stage			0.119
0/1/2	40 (46.5%)	12 (30.8%)	
3/4	46 (53.5%)	27 (69.2%)	
ypN stage			> 0.999
0	65 (75.6%)	29 (74.4%)	
1/2	21 (24.4%)	10 (25.6%)	
AJCC pathologic staging			0.828
pCR/I/II	64 (74.4%)	28 (71.8%)	
III/IV	22 (25.6%)	11 (28.2%)	
Complication by Dindo classification			0.542
1/2	78 (90.7%)	34 (87.2%)	
3/4	8 (9.3%)	5 (12.8%)	

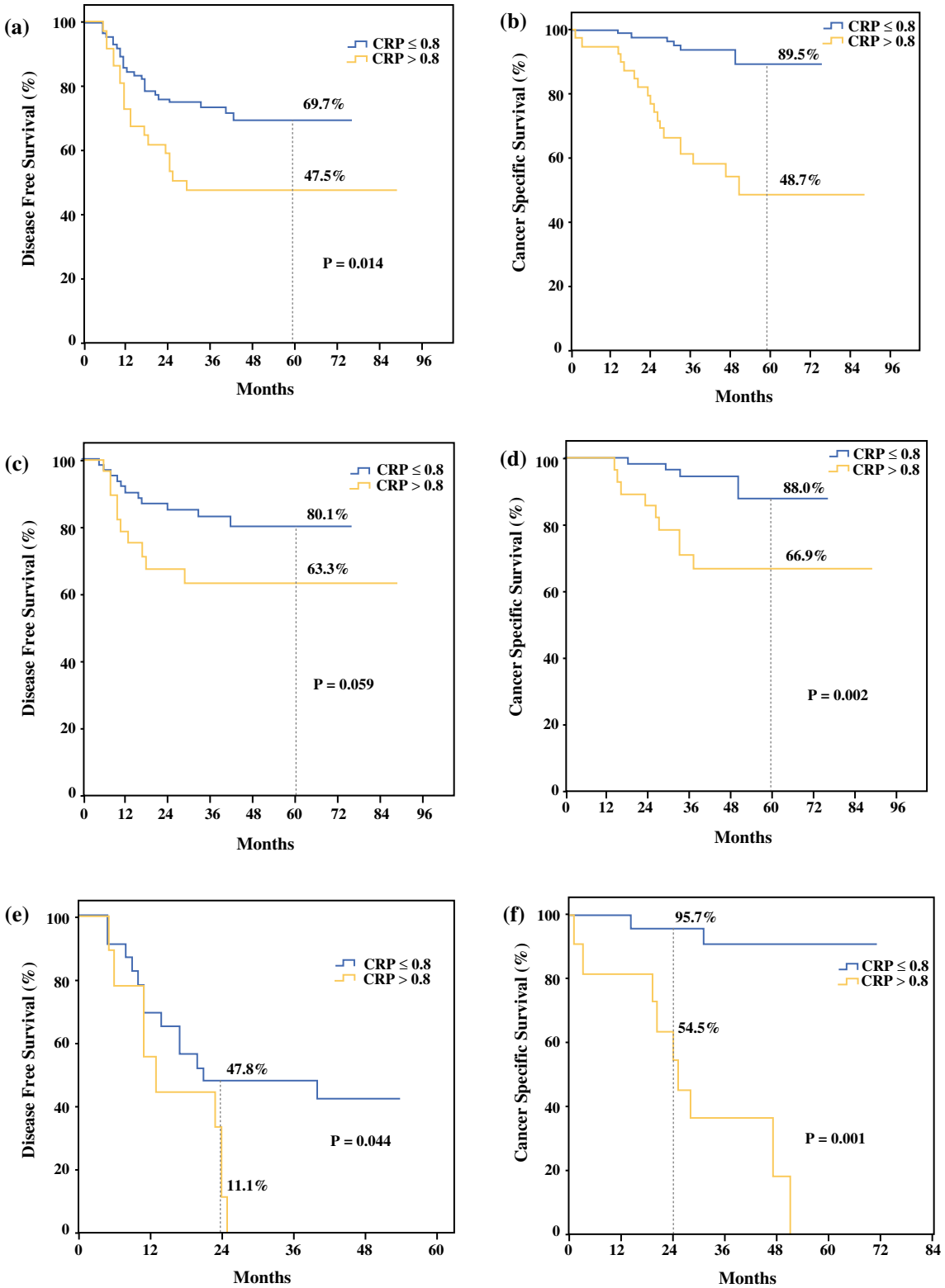

FIG. 1 Kaplan-Meier estimate and log rank test for CRP of (**a**, **b**) 125 patients, (**c**, **d**) 91 patients with ypN(-),(**e**, **f**) 34 patients with ypN(+) who underwent preoperative chemoradiation for rectal cancer

TABLE 2 Uni- and Multivariate analysis of risk factors for disease free survival and cancer specific survival in 125 patients who underwent preoperative chemoradiation for rectal cancer

Factors	Disease free survival				Cancer-specific survival			
	Uni-	Multivariate			Uni-	Multivariate		
	P value	HR	95% CI	*P* value	*P* value	HR	95% CI	*P* value
Age (< 65 vs. ≥ 65 years)	0.459				0.024	4.417	1.771–11.015	0.001
Gender (male vs. female)	0.850				0.861			
BMI (< 25 vs. ≥ 25 kg/m^2)	0.023	0.301	0.091–0.990	0.048	0.675			
Serum CEA (< 5 vs. ≥ 5 ng/mL)	0.436				0.382			
Histology (Well/Mod vs. Poor/Mucinous)	0.004	3.121	1.292–7.541	0.011	0.001			
ypT stage (0/1/2 vs. 3/4)	0.018							
ypN stage [ypN(−) vs. ypN(+)]	0.001	2.840	1.492–5.405	0.001	0.041			
Pathologic TNM staging (pCR/I/II vs. III/IV)	0.001				0.019	4.836	1.896–12.331	0.001
Complication by Dindo (< 3 vs. ≥ 3)	0.484				0.023			
CRP (≤ 0.8 vs. > 0.8 mg/dL)	0.014				0.001	9.261	3.495–24.543	0.001

1.492–5.405, $P = 0.001$), poor histological grade (HR = 3.121, 95% CI 1.292–7.541, $P = 0.011$), and low BMI (HR = 0.301, 95% CI 0.091–0.990, $P = 0.048$) were independent predictors of DFS. However, for CSS, preoperative CRP level (HR = 9.261, 95% CI 3.495–24.543, $P = 0.001$) was the strongest prognostic factor (Table 2).

In subgroup analysis, patients were classified into two groups based on the postoperative pathological nodal status (ypN − vs. ypN +). In each group, patients were further divided on the basis of preoperative CRP level (normal vs. elevated). In the ypN − subgroup, patients with elevated CRP levels showed significantly lower 5-year CSS (88.0 vs. 66.9%, $P = 0.002$) and poorer 5-year DFS tendency (80.1 vs. 63.3%, $P = 0.059$) than the patients with normal CRP levels (Fig. 1c, d). Similarly, in the ypN + subgroup, patients with elevated CRP levels were associated with significantly poorer DFS and CSS than were patients with normal CRP levels (median DFS, 11 vs. 21 months, $P = 0.044$; median CSS 25 vs. 43 months, $P = 0.001$; Fig. 1e, f). Multivariate analyses using the Cox proportional hazards model showed that CRP was an independent prognostic marker for survival in both subgroups (ypN −: HR 4.312, 95% CI 1.274–14.593, $P = 0.019$; ypN + : HR 5.727, 95% CI 1.251–26.216, $P = 0.025$) but not for DFS (Table 3).

We performed univariate and multivariate analyses to identify predictive factors associated with poor response after pCRT. The data revealed that patients with elevated CRP after pCRT were associated with poor tumor response [odds ratio (OR) 3.666, 95% CI 1.341–10.021, $P = 0.011$; Table 4].

DISCUSSION

C-reactive protein is the first acute-phase protein to be described in the literature and is a useful systemic biomarker of inflammation and tissue damage. CRP is rapidly produced in the hepatocytes and is principally regulated at the transcriptional level by the cytokine interleukin-6 (IL-6). Characteristically, CRP values remain constant but are significantly affected by the liver failure and other pathologies that provide an acute-phase stimulus.[9]

Currently, the role of chronic inflammation in tumorigenesis and tumor progression is widely accepted. Coussens et al.[1] showed that the pro-inflammatory factor COX-2 is expressed by stromal cells in early tumors and by the dysplastic epithelium in larger tumors. In our previous case study, we showed that rectal cancer patients overexpressing COX-2 were less likely to respond to preoperative chemoradiation.[19] Moreover, regular use of nonsteroidal anti-inflammatory drugs (NSAIDs) is associated with a reduced incidence of colorectal and other cancers, thereby suggesting a key role for inflammation in tumorigenesis.[20,21]

Tumor cells produce various cytokines and chemokines that attract leukocytes, which activate tissue remodeling and neo-angiogenesis, thereby creating a microenvironment suitable for tumor progression. Chronic inflammation in the tumor microenvironment is primarily induced by intratumoral or peritumoral recruitment of tumor-infiltrating lymphocytes (TILs) and tumor-associated macrophages (TAMs, M2), which are derived from monocytic precursors circulating in the blood and are known to play pivotal roles in tumor progression.[2,22,23]

TABLE 3 Uni- and multivariate analysis of risk factors for disease free survival and cancer specific survival in ypN(−) (*N* = 91) and ypN(+) (*N* = 34)

Factors	ypN(-) (N = 91)						ypPN(+) (N = 34)					
	Disease free survival				Cancer-specific survival				Disease free survival		Cancer-specific survival			
	Uni-	Multivariate			Uni-	Multivariate			Uni		Uni-	Multivariate		
	P value	HR	95% CI	*P* value	*P* value	HR	95% CI	*P* value	*P* value		*P* value	HR	95% CI	*P* value
Age (< 65 vs ≥ 65 years)	0.849				0.045	3.964	1.183–13.276	0.026	0.772		0.113			
Gender (male vs. female)	0.238				0.674				0.084		0.961			
BMI (< 25 vs. ≥ 25 kg/m^2)	0.083				0.501				0.373		0.382			
Serum CEA (< 5 vs. ≥ 5 ng/mL)	0.836				0.486				0.817		0.135			
Histology (Well/Mod vs. Poor/Mucinous)	0.002	7.190	2.209–23.398	0.001	0.011	3.824	0.977–14.971	0.054	0.315		0.034			
ypT stage (0/1/2 vs. 3/4)	0.073				0.123				0.733		0.397			
Complication by Dindo (< 3 vs. ≥ 3)	0.683				0.942				0.984		0.015	20.013	3.8832–104.534	0.001
CRP (≤ 0.8 vs. > 0.8 mg/dL)	0.059				0.002	4.312	1.274–14.593	0.019	0.044		0.001	5.727	1.251–26.216	0.025

Therefore, the measurement of serum CRP levels helps clinicians to predict tumor status. High CRP levels are induced by cytokines, such as IL-6, in the tumor and the tumor microenvironment and are strongly associated with poor prognosis in various types of cancer.[3,5,7,8,10,11,15,24,25]

Preoperative chemoradiotherapy (pCRT) is generally accepted as a standard treatment in locally advanced rectal cancer and dramatically affects the tumor microenvironment. Cengiz et al.[26] reported significant rise in CRP levels at the end of radiotherapy compared to pre-radiation period in patients with the diagnosis of endometrium and cervical cancer, and this finding reflected that chemoradiation itself induced inflammatory responses. However, it is difficult to distinguish whether elevated CRP in pCRT is caused by chemoradiation-induced inflammatory response or remnant tumor burdens, which would promote to release various peritumoral cytokines. Although local irradiation directly kills tumor cells by inducing extensive DNA damage, the surviving tumor cells with misrepaired DNA, and the surrounding irradiated stroma can induce tumor progression and increase the probability of distant metastasis by releasing protumoral cytokines.[27] Timaner et al.[28] reported that irradiated mice with implanted colon cancers showed recruitment of TAMs and remodeling of the tumor microenvironment, which promoted tumor regrowth and distant metastasis. Moreover, emerging evidence indicates that recurrence after radiation therapy shows a more aggressive tumor behavior and poor prognosis, known as the tumor bed effect, which suggests adaptation to the local hypoxic condition, as well as the selection of tumor cells with increased invasive characteristics.[29,30]

Therefore, analysis of the tumor and its microenvironment is critical to predict local and systemic recurrence after pCRT in rectal cancer. Although CRP is a nonspecific inflammatory marker, it can be a simple indicator of tumor prognosis, because increased cytokine release subsequently stimulates tumor growth in its microenvironment which, in turn, increases CRP levels.

Several studies have suggested that serum CRP or measured mGPS (modified Glasgow prognostic score) before CRT was associated a poor prognosis. For example, Dreyer et al.[31] reported that mGPS ($P = 0.022$) was associated with a poor pathologic response to pCRT. Toiyama et al.[16] identified an elevated CRP as a promising and independent prognostic factor in patients with rectal cancer treated by CRT. However, we could not find any studies that evaluated the relationship between pCRT and serum CRP before surgery. We hypothesized that interval periods between pCRT and surgery could promote remnant tumors adapting to the local hypoxic condition in some patients, leading to increased invasiveness.

TABLE 4 Logistic regression analysis and estimating odds ratio (ORs) for predicting tumor response (TRG4–5) in 125 patients who underwent chemoradiation for rectal cancer

Factors	Univariate			Multivariate		
	ORs	95% CI	*P* value	ORs	95% CI	*P* value
Age (< 65 vs. ≥ 65 years)	1.714	0.641–4.585	0.283			
Gender (male vs. female)	1.027	0.379–2.778	0.959			
BMI (< 25 vs. ≥ 25 kg/m^2)	0.747	0.229–2.441	0.630			
Serum CEA (< 5 vs. ≥ 5 ng/mL)	0.722	0.282–1.847	0.496			
Histology (Well/Mod vs. Poor/Mucinous)	3.667	0.755–17.810	0.107			
ypT stage (0/1/2 vs. 3/4)	6.705	1.868–21.887	0.006	5.584	1.514–20.597	
ypN stage [ypN(−) vs. ypN(+)]	1.190	0.417–3.397	0.745			
CRP (≤ 0.8 vs. > 0.8 mg/dL)	4.036	1.538–10.592	0.005	3.666	1.341–10.021	0.011

Our study demonstrated that elevated CRP levels after pCRT were associated with poor prognosis regardless of the TNM stage, thereby supporting the aforementioned radiation-induced tumor progression theory. In subgroup analysis of ypN − patients, the elevated CRP group showed poorer DFS and CSS than the normal group (5-year DFS, 63.3 vs. 80.1%, $P = 0.059$; 5-year CSS, 66.9 vs. 88.0%, $P = 0.002$, respectively; Fig. 1c, d). Moreover, preoperative CRP level was one of the strongest predicting markers for survival in ypN − pateints (HR 4.312, 95% CI 1.274–14.593, $P = 0.019$; Table 3). In ypN + patients, normal CRP level was associated with good prognosis. Patients belonging to elevated and normal CRP group showed significant differences in survival (2-year CSS. 95.7 vs. 54.5%, $P = 0.001$; Fig. 1f). There are two possible explanations for this result. Increased CRP levels after pCRT may be attributable to the surviving hypoxia-resistant invasive cancer cells or a result of accelerated local and systemic metastasis because of radiation-induced remodeling of the tumor microenvironment.

Our findings are significant for clinical application, because at present, there are no reliable tools for predicting systemic recurrence or prognosis. The presently used imaging methods, and TNM stage are limited in predicting systemic recurrence. Therefore, estimating CRP levels could help clinicians determine whether patients need additional therapy to reduce systemic failure during the waiting period between completion of pCRT and curative surgery. Our results suggest that the "intensified chemotherapy strategies", which are currently undergoing randomized trials, need to be seriously considered for patients with elevated CRP levels after pCRT.[32–34]

Our study also showed an association between elevated CRP and poor TRG (Table 4). These findings are clinically relevant in predicting preoperative tumor response when combined with the radiological assessment. Interestingly, 12% of patients with normal CRP showed poor tumor response (TRG4–5; Table 1). This suggests that normal CRP level does not guarantee good tumor response.

The retrospective design of this study had several potential drawback because of a small sample size. Moreover, we did not compare CRP levels at different points of pCRT application, such as pre-pCRT, preoperation, and postoperation to observe the overall changes in CRP levels and consider its effects on prognosis. Therefore, further large-scale, prospective studies are needed to verify these issues and to determine the clinical application of CRP in the future.

CONCLUSIONS

Our study demonstrates that elevated preoperative CRP level after chemoradiation is strongly associated with poor survival outcomes and reduced tumor regression in rectal cancer patients. Therefore, CRP shows promise as a potential prognostic marker in rectal cancer patients who have undergone chemoradiotherapy.

ACKNOWLEDGEMENT This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) and funded by the Korea Government (Ministry of Science, ICT and Future Planning, MSIT; Grant No. 2017R1C1B5076797).

DISCLOSURE The authors declare that they have no conflicts of interest.

REFERENCES

1. Coussens LM, Werb Z. Inflammation and cancer. *Nature.* 2002;420(6917):860–7.
2. Vakkila J, Lotze MT. Inflammation and necrosis promote tumour growth. *Nat Rev Immunol.* 2004;4(8):641–8.

3. Crumley AB, McMillan DC, McKernan M, Going JJ, Shearer CJ, Stuart RC. An elevated C-reactive protein concentration, prior to surgery, predicts poor cancer-specific survival in patients undergoing resection for gastro-oesophageal cancer. *Br J Cancer.* 2006;94(11):1568–71.
4. Heikkila K, Ebrahim S, Lawlor DA. A systematic review of the association between circulating concentrations of C reactive protein and cancer. *J Epidemiol Community Health.* 2007;61(9):824–33.
5. Kim DK, Oh SY, Kwon HC, et al. Clinical significances of preoperative serum interleukin-6 and C-reactive protein level in operable gastric cancer. *BMC Cancer.* 2009;9:155.
6. Leitch EF, Chakrabarti M, Crozier JE, et al. Comparison of the prognostic value of selected markers of the systemic inflammatory response in patients with colorectal cancer. *Br J Cancer.* 2007;97(9):1266–70.
7. Nagaoka S, Yoshida T, Akiyoshi J, et al. Serum C-reactive protein levels predict survival in hepatocellular carcinoma. *Liver Int.* 2007;27(8):1091–7.
8. Pine SR, Mechanic LE, Enewold L, et al. Increased levels of circulating interleukin 6, interleukin 8, C-reactive protein, and risk of lung cancer. *J Natl Cancer Inst.* 2011;103(14):1112–22.
9. Pepys MB, Baltz ML. Acute phase proteins with special reference to C-reactive protein and related proteins (pentaxins) and serum amyloid A protein. *Adv Immunol.* 1983;34:141–212.
10. Nozoe T, Matsumata T, Kitamura M, Sugimachi K. Significance of preoperative elevation of serum C-reactive protein as an indicator for prognosis in colorectal cancer. *Am J Surg.* 1998;176(4):335–8.
11. Canna K, McArdle PA, McMillan DC, et al. The relationship between tumour T-lymphocyte infiltration, the systemic inflammatory response and survival in patients undergoing curative resection for colorectal cancer. *Br J Cancer.* 2005;92(4):651–4.
12. Dreanic J, Maillet M, Dhooge M, et al. Prognostic value of the Glasgow Prognostic Score in metastatic colorectal cancer in the era of anti-EGFR therapies. *Med Oncol.* 2013;30(3):656.
13. Fukuchi M, Kuwabara K, Tsuji Y, et al. C-reactive protein is a negative independent factor in patients with stage IV colorectal cancer undergoing oxaliplatin-based chemotherapy. *Anticancer Res.* 2013;33(11):5051–5.
14. Lin M, Huang J, Zhu J, Shen H. Elevated pre-treatment levels of high sensitivity C-reactive protein as a potential prognosticator in patients with colorectal cancer. *Exp Ther Med.* 2013;6(6):1369–74.
15. Roxburgh CS, Salmond JM, Horgan PG, Oien KA, McMillan DC. The relationship between the local and systemic inflammatory responses and survival in patients undergoing curative surgery for colon and rectal cancers. *J Gastrointest Surg.* 2009;13(11):2011–8 **(discussion 2018–9)**.
16. Toiyama Y, Inoue Y, Saigusa S, et al. C-reactive protein as predictor of recurrence in patients with rectal cancer undergoing chemoradiotherapy followed by surgery. *Anticancer Res.* 2013;33(11):5065–74.
17. Toiyama Y, Fujikawa H, Koike Y, et al. Evaluation of preoperative C-reactive protein aids in predicting poor survival in patients with curative colorectal cancer with poor lymph node assessment. *Oncol Lett.* 2013;5(6):1881–8.
18. Mandard AM, Dalibard F, Mandard JC, et al. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations. *Cancer.* 1994;73(11):2680–6.
19. Min BS, Choi YJ, Pyo HR, et al. Cyclooxygenase-2 expression in pretreatment biopsy as a predictor of tumor responses after preoperative chemoradiation in rectal cancer. *Arch Surg.* 2008;143(11):1091–7 **(discussion 1097)**.
20. Giovannucci E, Egan KM, Hunter DJ, et al. Aspirin and the risk of colorectal cancer in women. *N Engl J Med.* 1995;333(10):609–14.
21. Gonzalez-Perez A, Garcia Rodriguez LA, Lopez-Ridaura R. Effects of non-steroidal anti-inflammatory drugs on cancer sites other than the colon and rectum: a meta-analysis. *BMC Cancer.* 2003;3:28.
22. Naito Y, Saito K, Shiiba K, et al. CD8 + T cells infiltrated within cancer cell nests as a prognostic factor in human colorectal cancer. *Cancer Res.* 1998;58(16):3491–4.
23. Arenberg DA, Keane MP, DiGiovine B, et al. Macrophage infiltration in human non-small-cell lung cancer: the role of CC chemokines. *Cancer Immunol Immunother.* 2000;49(2):63–70.
24. Redmond HP. Systemic inflammatory response predicts survival following curative resection of colorectal cancer (Br J Surg 2003;90:215–9). *Br J Surg.* 2003;90(7):889 (**author reply 889**).
25. Shiu YC, Lin JK, Huang CJ, et al. Is C-reactive protein a prognostic factor of colorectal cancer? *Dis Colon Rectum.* 2008;51(4):443–9.
26. Cengiz M, Akbulut S, Atahan IL, Grigsby PW. Acute phase response during radiotherapy. *Int J Radiat Oncol Biol Phys.* 2001;49(4):1093–6.
27. Barcellos-Hoff MH. Integrative radiation carcinogenesis: interactions between cell and tissue responses to DNA damage. *Semin Cancer Biol.* 2005;15(2):138–48.
28. Timaner M, Bril R, Kaidar-Person O, et al. Dequalinium blocks macrophage-induced metastasis following local radiation. *Oncotarget.* 2015;6(29):27537–54.
29. Ruegg C, Monnier Y, Kuonen F, Imaizumi N. Radiation-induced modifications of the tumor microenvironment promote metastasis. *Bull Cancer.* 2011;98(6):47–57.
30. Barker HE, Paget JT, Khan AA, Harrington KJ. The tumour microenvironment after radiotherapy: mechanisms of resistance and recurrence. *Nat Rev Cancer.* 2015;15(7):409–25.
31. Dreyer SB, Powell AG, McSorley ST, et al. The pretreatment systemic inflammatory response is an important determinant of poor pathologic response for patients undergoing neoadjuvant therapy for rectal cancer. *Ann Surg Oncol.* 2017;24(5):1295–303.
32. Klautke G, Foitzik T, Ludwig K, Klar EJM, Fietkau R. Intensified neoadjuvant chemoradiotherapy (CRT) with capecitabine and irinotecan in patients with locally advanced rectal cancer (LARC): A phase I/II study. *J Clin Oncol.* 2004;22(14_Suppl):3693-3.
33. Gerard JP, Azria D, Gourgou-Bourgade S, et al. Comparison of two neoadjuvant chemoradiotherapy regimens for locally advanced rectal cancer: results of the phase III trial ACCORD 12/0405-Prodige 2. *J Clin Oncol.* 2010;28(10):1638–44.
34. Rödel C, Graeven U, Fietkau R, et al. Oxaliplatin added to fluorouracil-based preoperative chemoradiotherapy and postoperative chemotherapy of locally advanced rectal cancer (the German CAO/ARO/AIO-04 study): final results of the multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol.* 2015;16(8):979–89.