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Which Is a More Reliable Indicator of Survival After Gastric Cancer Surgery: Postoperative Complication Occurrence or C-Reactive Protein Elevation?

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Background and Objectives: The impact of postoperative complications on long-term outcome has been reported in several types of malignancies. However, it is unclear why postoperative complications affect long-term outcome. The aim of this study is evaluating whether postoperative complication occurrence or C-reactive protein (CRP) elevation better reflects long-term outcome in gastric cancer patients.

Methods: This study included 305 patients who underwent curative surgery for pT2–T4b gastric cancer. Patients were divided into two groups based on the peak CRP value (CRP_{max}): low (<12 mg/dl) and high CRP_{max} (≥12 mg/dl). A multivariate analysis was conducted to identify independent prognostic factors for recurrence-free survival (RFS).

Results: Postoperative complications (≥Grade II) occurred in 86 of 305 patients (28.2%). Although CRP elevation ($P = 0.001$) and postoperative complication occurrence ($P = 0.045$) was each significantly associated with RFS in the univariate analysis, multivariate analysis identified CRP elevation ($P = 0.017$) but not complication occurrence ($P = 0.682$) as an independent prognostic factor. Among patients without complications, those in the high CRP_{max} group had significantly worse RFS than those in the low CRP_{max} group ($P = 0.004$).

Conclusions: CRP elevation is a more reliable indicator of survival after gastric cancer surgery than postoperative complication occurrence. Surgeons should minimize the postoperative inflammatory response to improve prognosis.

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KEY WORDS: gastric cancer; gastrectomy; C-reactive protein; postoperative complication

INTRODUCTION

Gastric cancer is a major cause of cancer-related deaths worldwide; it is the most common cause in eastern Asia [1]. Gastrectomy is necessary to cure patients with gastric cancer, although recurrence can be observed even after curative surgery for gastric cancer [2–5]. Tumor stage as defined in the International Union Against Cancer (UICC) or Japanese Gastric Cancer Association (JGCA) classification system is a well-established long-term prognostic factor; other prognostic factors have been identified [2,3,6].

Previous studies have shown that the occurrence of postoperative complications, especially anastomotic leakage, could have a significant negative impact on recurrence and survival in patients with colorectal, esophageal, or breast cancer [7–15]. Furthermore, some studies have found an association between anastomotic leakage and higher distant recurrence rates [16,17]. This association between postoperative complication occurrence and negative prognosis was also confirmed in recent studies on gastric cancer [18–23]. However, it is unclear why the occurrence of postoperative complications affects long-term outcome.

We hypothesized that the release of systemic cytokines induced during a postoperative complication stimulates residual cancer cell growth. We focused on postoperative inflammatory response, serum C-reactive protein (CRP) levels in particular, because CRP reflects the systemic inflammatory response, including interleukin (IL)-6 elevation. CRP is secreted by the liver upon stimulation by IL-6; it has been reported that serum CRP and IL-6 levels are closely correlated [24,25]. Thus, we consider serum CRP concentration to be a useful indicator of increased levels of postoperative inflammatory cytokines. Some recent reports showed that the preoperative systemic inflammatory response, as evaluated by elevated CRP concentration and hypoalbuminemia, was an independent prognostic factor in patients with operable gastric cancer [26,27], whereas no previous study have investigated the relationship between postoperative CRP elevation and postoperative outcome. The aim of this study was to evaluate whether postoperative complication status or CRP elevation is a more reliable indicator of survival after curative gastric cancer surgery.

METHODS

Patients

This retrospective study included 305 consecutive patients with pT2-T4b gastric cancer who underwent gastrectomy at Osaka University Hospital between February 2001 and December 2012. Tumor staging was based on the seventh edition of the UICC classification system. Patients with stage IV disease, non-curative resection (R1–2), or preoperative chemotherapy were excluded. In general, gastrectomy and lymph node dissection were carried out according to the Japanese Gastric Cancer Treatment Guidelines [28]. Patients were followed every 3–6 months after surgery until recurrence. This study was approved by the institutional review board of the Osaka University Hospital.

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Evaluations

All patients were observed postoperatively for any complications until discharge from the hospital. The severity of postoperative complications were evaluated according to the Clavien-Dindo classification system [29,30]. We considered complications of Grade II or higher as postoperative complications in this study. When two or more complications occurred in one patient, the higher grade was used.

To evaluate the systemic postoperative inflammatory response, serum CRP levels were measured on postoperative days (PODs) 1, 3, 5, and 7 in principle, and additional measurements were conducted based on patient condition. The highest serum CRP level from surgery until hospital discharge was defined as CRP_{max}.

Statistics

Recurrence-free survival (RFS) was defined as the time from surgery to either the first recurrence or death from any cause. Clinicopathological characteristics and laboratory data were compared using the χ^2 test for categorical variables and the Mann–Whitney *U*-test for continuous variables. Cumulative survival was plotted using the Kaplan–Meier method, and differences were compared using the log-rank test. Cox proportional hazards models were used for both univariate and multivariate analyses, and multivariate analysis used the factors with $P < 0.1$ in the univariate analysis. Hazard ratios (HR) are reported with 95% confidence intervals (CI). *P*-values <0.05 were considered statistically significant. Statistical analyses were performed using the SPSS statistical package, version 22.0 (SPSS, Chicago, IL).

RESULTS

Among the 305 patients, postoperative complications of Grade II or higher occurred in 86 patients (28.2%). The most frequent complication was pancreatic fistula in 24 patients (7.8%), followed by abdominal abscess in 18 (5.9%) and anastomotic leakage in 11 (3.6%). Since the median CRP_{max} value was 11.7 mg/dl (range, 1.2–40.9 mg/dl), patients were divided into a low CRP_{max} group and a high CRP_{max} group with the threshold of 12 mg/dl. The baseline characteristics of the 305 patients are shown in Table I. The high CRP_{max} group consisted of a significantly higher proportion of male patients and those who underwent total gastrectomy, and had higher body mass index, longer operative time, more blood loss, and postoperative complications than the low CRP_{max} group. There were no significant differences in pT status, pN status, and pStage between the two groups.

The RFS curves according to CRP_{max} group are shown in Figure 1. The median follow-up duration was 57 months for the censored cases. RFS in the high CRP_{max} group was significantly worse than that in the low CRP_{max} group (log-rank $P = 0.001$). During follow-up, 81 patients (26.6%) developed recurrence (39 in the peritoneum, 28 in the liver, 13 in the lymph nodes, 8 in other sites) and 18 patients (5.9%) died from other diseases (Table II). The high CRP_{max} group had significantly more recurrence ($P = 0.012$) and more mortality from other diseases ($P = 0.010$).

TABLE I. Clinicopathological Characteristics According to the Peak Serum CRP Concentration (CRP_{max})

Variable	Low CRP_{max} (n = 157)	High CRP_{max} (n = 148)	*P*-value
Age, years			0.194
Median (range)	66 (30–92)	68.5 (35–87)	
Sex			<0.001
Male	95 (60.5%)	118 (79.7%)	
Female	62 (39.5%)	30 (20.3%)	
Body mass index, kg/m^2			<0.001
Median (range)	21.6 (12.9–44.0)	23.2 (13.3–31.3)	
Approach			0.178
Open	100 (63.7%)	105 (70.9%)	
Laparoscopic	57 (36.3%)	43 (29.1%)	
Type of gastrectomy			<0.001
Total	41 (26.1%)	70 (47.3%)	
Subtotal	116 (73.9%)	78 (52.7%)	
Lymph node dissection			0.719
D1+	41 (26.1%)	36 (24.3%)	
D2	116 (73.9%)	112 (75.7%)	
Operation time, min			<0.001
Median (range)	205 (100–345)	228.5 (107–457)	
Blood loss, ml			<0.001
Median (range)	250 (0–3100)	475 (20–2250)	
Adjuvant chemotherapy			0.940
No	98 (62.4%)	93 (62.8%)	
Yes	59 (37.6%)	55 (37.2%)	
pT status			0.089
T2	64 (40.8%)	44 (29.7%)	
T3	62 (39.5%)	63 (42.6%)	
T4	31 (19.7%)	41 (27.7%)	
pN status			0.624
N0	71 (45.2%)	68 (45.9%)	
N1	26 (16.6%)	32 (21.6%)	
N2	34 (21.7%)	27 (18.2%)	
N3	26 (16.6%)	21 (14.2%)	
pStage			0.655
I	33 (21.0%)	25 (16.9%)	
II	68 (43.3%)	68 (45.9%)	
III	56 (35.7%)	55 (37.2%)	
Postoperative complication			<0.001
No	136 (86.6%)	83 (56.1%)	
Yes	21 (13.4%)	65 (43.9%)	

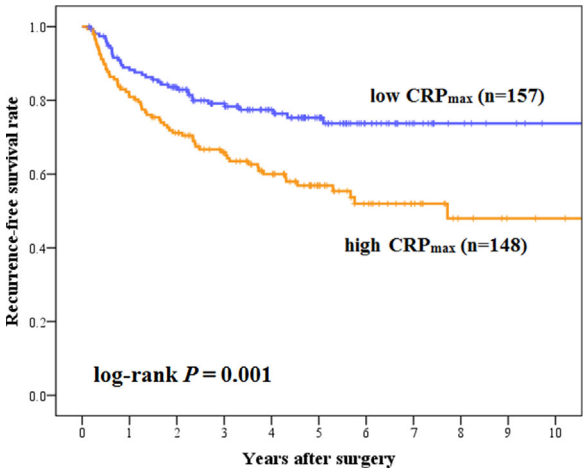

Fig. 1. Kaplan–Meier recurrence-free survival in the low (<12 mg/dl) and high CRP_{max} (≥12 mg/dl) groups.

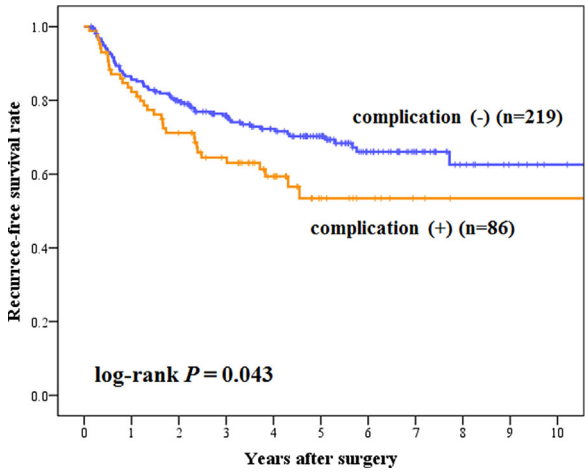

Fig. 2. Kaplan–Meier recurrence-free survival between patients with and without postoperative complications.

Patients with and without postoperative complications also differed significantly in RFS (log-rank $P = 0.043$) (Fig. 2). To evaluate the possible effect of confounding between CRP elevation and postoperative complication occurrence, we conducted a survival analysis after stratification by the presence or absence of postoperative complications. The difference in RFS between the low and high CRP_{max} groups was not statistical significant (log-rank $P = 0.492$) in patients with postoperative complications (Fig. 3), while patients without postoperative complications in the high CRP_{max} group had significantly worse RFS than their counterparts in the low CRP_{max} group (log-rank $P = 0.004$) (Fig. 4).

We analyzed 13 potentially prognostic factors associated with RFS using univariate analysis (Table III). Although both CRP elevation ($P = 0.001$) and postoperative complication occurrence ($P = 0.045$) were significantly associated with RFS in the univariate analysis, the HR for recurrence (1.99, 95% CI 1.32–2.99) on CRP elevation was higher than that (1.53, 95% CI 1.01–2.32) on postoperative complication occurrence. The multivariate analysis identified CRP elevation ($P = 0.017$) but not postoperative complication occurrence ($P = 0.682$) as an independent prognostic factor, in addition to pT status ($P = 0.007$) and pN status ($P < 0.001$) (Table III).

DISCUSSION

Our study revealed that postoperative CRP elevation could predict RFS in patients after curative surgery for gastric cancer. Postoperative CRP elevation was associated with increases in both recurrence and death by other diseases. Several previous studies have revealed that postoperative complications have a significant negative impact on recurrence and prognosis [7–23]. Indeed, our study showed the occurrence of postoperative complications was a significant prognostic factor in the univariate analysis. However, our multivariate analysis showed that CRP elevation but not postoperative complication occurrence was an independent prognostic factor, and that RFS was significantly affected by CRP elevation even if complications did not occur after surgery. These results imply that surgery producing high systemic inflammatory response leads to poor outcome in prognosis even if postoperative complication does not occur.

It is well known that the preoperative systemic inflammatory response is associated with poor outcomes after curative surgery for various types of malignancies [26,27,31]. A preoperative inflammatory response may simply reflect tumor necrosis or local tissue damage. On the other hand, there are only a very limited number of studies demonstrating that the postoperative inflammatory response affects prognosis after curative surgery. Two retrospective studies showed that a sustained increase in CRP is an independent negative prognostic factor after curative surgery for colorectal cancer [17,32]. Recently, Matsuda et al. have reported that persistent CRP elevation after

TABLE II. Events of Recurrence-Free Survival

Variable	Low CRP_{max} (n = 157)	High CRP_{max} (n = 148)	*P*-value
Recurrence	32 (20.4%)	49 (33.1%)	0.012
Peritoneum	17 (10.8%)	22 (14.9%)	
Liver	10 (6.4%)	18 (12.2%)	
Lymph node	3 (1.9%)	10 (6.8%)	
Others	3 (1.9%)	5 (3.4%)	
Death by other diseases	4 (2.5%)	14 (9.5%)	0.010

CRP_{max}, the peak serum CRP concentration. The number of patients in each site of recurrence can be duplicated.

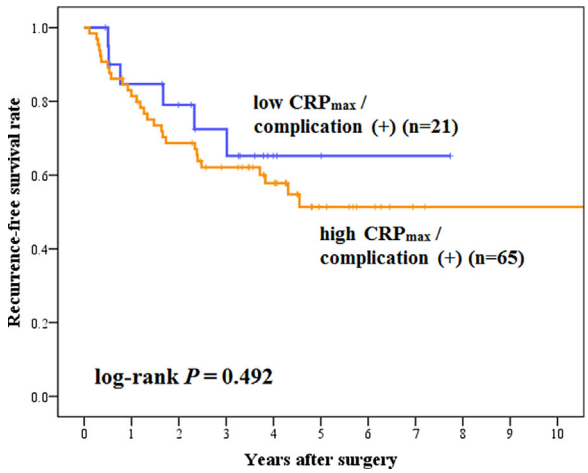

Fig. 3. Kaplan–Meier recurrence-free survival between patients with postoperative complications in the low (<12 mg/dl) and high CRP_{max} (≥12 mg/dl) groups.

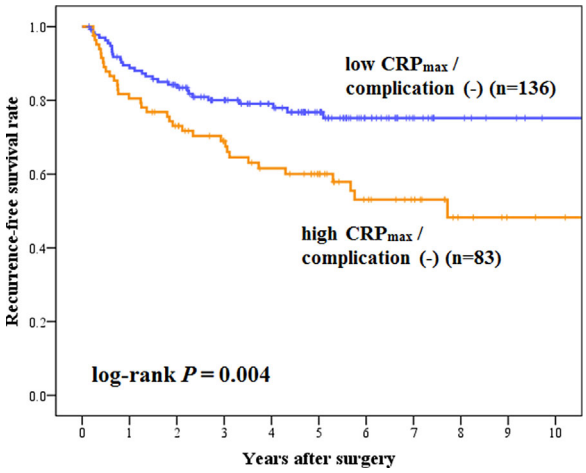

Fig. 4. Kaplan–Meier recurrence-free survival between patients without postoperative complications in the low (<12 mg/dl) and high CRPmax (≥12 mg/dl) groups.

esophagectomy was a significant prognostic factor in patients with esophageal cancer [33]. To the best of our knowledge, however, no previous studies have investigated the influence of the peak CRP value during the postoperative period on recurrence after adjustment for the presence or absence of postoperative complications. Our study showed that the peak CRP value during the early postoperative recovery phase affects RFS even in the patients without postoperative complications. Although white blood cell count is a frequently used marker of the inflammatory response, it was not significantly associated with RFS (data not shown). These results imply that the peak CRP value during the early postoperative recovery phase could be useful not only for the detection of surgical site infections but also for the prediction of long-term outcomes. A large-scale prospective study is needed to validate the clinical usefulness of postoperative CRP evaluation in gastric cancer.

It is unclear why the postoperative inflammatory response affects long-term outcome. Two mechanisms have been proposed to explain how early recurrence may be induced by the postoperative systemic inflammatory response. One possible mechanism is growth stimulation of residual cancer cells by soluble factors induced by the inflammatory response. Salvans et al. reported that serum and abdominal fluid in patients with postoperative peritoneal infection enhanced tumor cell line migration and invasion in vitro [34]. These fluids may contain proinflammatory cytokines and growth factors, which are primarily synthesized after trauma and initially released locally by leukocytes, macrophages, and endothelial cells, and then released systemically [35–38]. IL-6 and IL-1β were shown to increase vascular endothelial growth factor (VEGF) expression in various cancer cell lines, and VEGF was reported to induce tumor angiogenesis leading to increase tumor recurrence in mice [39–42]. The inflammatory response releases soluble factors that may ultimately stimulate residual tumor cell growth. The other possible cause is host immunosuppression. It is well established that the inflammatory response is associated with host immunosuppression [43,44]. High levels of IL-6 can suppress the proliferation and function of cytotoxic T lymphocytes, natural killer cells, and dendritic cells, which may cause immune escape by cancer cells [45–47]. Residual tumor cells can grow in this postoperative period with host immunosuppression. Immunosuppression might cause death also by other diseases. Indeed, CRP elevation showed a trend toward increasing mortality from infectious diseases (Supplementary Table).

In Japan, adjuvant chemotherapy with S-1 for one year is the standard of care, since a large-scale phase III trial demonstrated the clinical benefit of postoperative S-1 for pStage II and III gastric cancer [48,49]. Although the absence of adjuvant chemotherapy may be associated with poor RFS in the high CRP_{max} group, adjuvant chemotherapy status was not a significant prognostic factor in the

TABLE III. Univariate and Multivariate Analyses of Prognostic Factors Associated With Recurrence-Free Survival After Gastric Surgery

	Univariate analysis		Multivariate analysis	
Characteristics	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age				
≥68 year	1.38 (0.93–2.05)	0.112		
Sex				
Male	1.41 (0.90–2.22)	0.136		
Body mass index				
<25 kg/m^2	1.11 (0.67–1.86)	0.675		
Approach				
Open	1.94 (1.21–3.12)	0.006	1.27 (0.75–2.16)	0.373
Type of gastrectomy				
Total	1.32 (0.89–1.97)	0.172		
Lymph node dissection				
D2	1.11 (0.70–1.76)	0.647		
Operation time				
≥240 min	1.39 (0.93–2.09)	0.107		
Blood loss				
≥400 ml	2.01 (1.35–2.99)	0.001	1.29 (0.80–2.07)	0.305
Adjuvant chemotherapy				
Yes	1.42 (0.95–2.11)	0.086	0.83 (0.55–1.27)	0.395
pT status				
T4	2.26 (1.50–3.42)	<0.001	1.81 (1.17–2.78)	0.007
pN status				
N1–N3	2.88 (1.85–4.48)	<0.001	2.81 (1.75–4.50)	<0.001
Postoperative complication				
Yes	1.53 (1.01–2.32)	0.045	1.10 (0.70–1.73)	0.682
CRP_{max}				
≥12 mg/dl	1.99 (1.32–2.99)	0.001	1.77 (1.11 –2.82)	0.017

HR, hazard ratio; CI, confidence interval; CRP_{max}, the peak serum CRP concentration.

multivariate analysis, indicating that the impact of adjuvant chemotherapy on this study was not clear.

In recent years, laparoscopic gastric cancer surgery has become common. Many clinical trials have evaluated the non-inferiority of laparoscopic surgery in terms of survival [50]. In general, laparoscopic gastrectomy is considered a less invasive procedure, which can reduce the postoperative inflammatory response and immunosuppression; namely, laparoscopic surgery may be associated with better prognosis compared to more invasive open surgery if the complication rate is not higher with laparoscopic surgery. In this study, RFS was worse in the open surgery group than in the laparoscopic group, with a HR of 1.27 in the multivariate analysis, although this association was not statistically significant. This implies that a better prognosis can be expected in the laparoscopic group, because the CRP_{max} value was significantly lower in the laparoscopic group (median, 11.1 mg/dl) than in the open surgery group (median, 12.1 mg/dl) ($P = 0.009$). Thus, our study suggested that less invasive surgery like laparoscopic surgery should be considered to reduce the postoperative systemic inflammatory response and improve long-term outcomes.

CONCLUSIONS

CRP elevation was a more reliable indicator of survival after gastric cancer surgery than postoperative complication occurrence. Surgeons should minimize the postoperative inflammatory response to improve long-term outcomes.

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