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ORIGINAL ARTICLE

Meaning of C-reactive protein around esophagectomy for cStage III esophageal cancer

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Abstract

Purpose The prognosis of esophageal cancer is dismal, and the 3-year overall survival of cStage III does not reach 50.0%. C-reactive protein (CRP) is a well-known protein that reflects the short- and long-term operative outcomes of esophageal cancer. However, since elevated CRP levels are often observed in cStage III esophageal cancer, whether or not CRP still reflects the prognosis is unclear.

Methods Eighty-four patients who were diagnosed with cStage III esophageal cancer and underwent R0/1 operation from January 2007 to December 2014 were retrospectively evaluated.

Results The mean age was 66.8 years, and the majority of patients were male. The median preoperative and postoperative CRP levels were 0.15 and 1.47 mg/dl, respectively. A majority of the patients underwent thoracoscopic surgery, and the median blood loss and operation duration were 456 ml and 11.6 h, respectively. Forty-six patients (54.8%) died during the observation period, and the 3-year overall survival was 52.4%. A multivariate analysis showed that the preoperative CRP level, postoperative albumin level, blood loss, and complications were independent prognostic factors. A multiple linear regression analysis showed that an elevated postoperative CRP level was affected by the operation duration and preoperative CRP levels.

Conclusions These findings suggest that the preoperative CRP level is a prognostic factor for cStage III esophageal cancer and that postoperative elevation in the CRP level is affected by the operation duration.

Keywords C-reactive protein · Esophageal cancer · Surgical stress

Introduction

Esophagectomy is one of the most invasive operative procedures and has the lowest 5-year survival rate among patients with gastroenterological cancer [1]. The 3-year survival rate dramatically decreases below 50.0% when the cStage is higher than III [2]. Furthermore, an even poorer survival rate is observed when the tumor invasion is deeper and more lymph node metastasis are noted [2]. However, there are some cStage III patients who have achieved a long-term survival.

Surgical stress is known to induce inflammatory cytokines [3–7], and C-reactive protein (CRP) is a well-known protein that is produced as a response to inflammatory cytokines [8]. Some reports have shown that the perioperative CRP level reflects the long-term outcomes after esophagectomy [9–12], and other reports have found that the postoperative CRP level reflects the short-term outcomes, such as infectious complications and anastomotic leakage [13, 14]. However, all stages of esophageal cancers were included in those studies. Since an elevated CRP level is known to be a response to secondary tumor necrosis and tumor damage [15], it might be more often observed in advanced-stage disease, which might affect these results. Furthermore, the factors affecting the postoperative CRP levels are still not clear.

Therefore, we conducted a retrospective study to clarify the role of CRP in the context of esophagectomy and to assess the factors affecting the elevation of the postoperative CRP level in cases of cStage III esophageal cancer.

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Patients and methods

Study population

Patients who had been diagnosed with cStage III esophageal cancer and undergone R0/1 esophagectomy at Kobe University Hospital from January 2007 to December 2014 were investigated in this study. The cStage was assessed based on esophagogastroduodenoscopy and computed tomography before treatment, and the TNM classification was determined according to the 7th edition of Union for International Cancer Control [16]. The clinicopathologic data extracted from the medical records included the age, sex, body mass index, hematological examination, tumor location, operation time, and blood loss. A preoperative hematological examination was performed within a week prior to surgery, and a postoperative hematological examination was performed just after the patient returned to the intensive-care unit, which was defined as postoperative day (POD) 0. Operative complications were graded according to the Clavien-Dindo classification, and cases with a classification of grade > III were defined as having operative complications [17].

All study participants provided their informed consent, and the study design was approved by the ethics review board at Kobe University Hospital and conforms to the provisions of the 1995 Declaration of Helsinki.

Surgical procedure

Surgical resection consisted of radical right thoracotomy or thoracoscopy with mediastinal and abdominal lymphadenectomy. Cervical lymphadenectomy was performed when the primary cancer was observed in the upper or middle esophagus according to the Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus from the Japan Esophageal Society [18]. A laparoscopic procedure was performed in the abdominal part whenever there was no suspicion of abdominal lymph node metastasis according to preoperative imaging findings. When abdominal lymph node metastasis was suspected, laparotomy was performed.

Antibiotics around operation

Cefazolin was intravenously injected prior to the operation and every 3 h after the last injection until the operation finished. No additional antibiotics were used after the operation, unless a new infection was confirmed.

Statistical analyses

The optimum cut-off level of CRP and albumin (Alb) were determined by a receiver operating characteristics (ROC) analysis. The survival time was calculated from the date of the first visit to our hospital to the occurrence of the event or the last known date of follow-up. Survival analyses were performed using the Kaplan–Meier method with the log-rank test. A Cox proportional hazard model was used to assess the predictors for the survival. A multiple linear regression analysis was used to assess the factors that affected the postoperative CRP levels. Variables with a P value < 0.2 in a univariate analysis were further evaluated in a multivariate analysis. In all analyses, a $P < 0.05$ was accepted as statistically significant. Descriptive statistics were obtained using the JMP statistical software package (JMP® 13; SAS Institute Inc., Cary, NC, USA).

Results

From January 2007 to December 2014, 267 patients underwent the operation of interest. Among them, 98 were diagnosed with cStage III disease, and 14 were excluded due to R2 resection. In total, 84 patients were investigated in this study (Fig. 1). The characteristics of the patients are listed in Table 1. The mean age was 66.8 ± 8.5 years old, the majority of the patients were male, the mean body mass index was 20.9 ± 3.4, and the main tumor was typically located in the lower thoracic. The tumor depth was clinical T3 in the majority of cases, and lymphatic metastasis was typically clinical N1. Seventy-seven patients (91.7%) received neoadjuvant chemotherapy (NAC). The median (range) preoperative and postoperative CRP levels were 0.15 (0.10–2.66) and

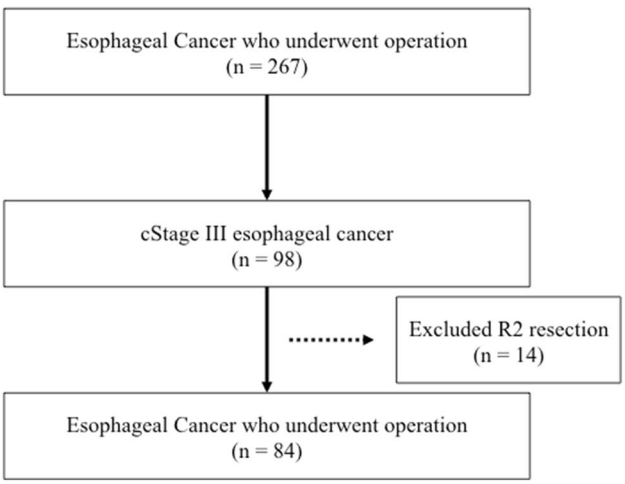

Fig. 1 Consort flow diagram of the study

Table 1 Characteristics and operative outcomes of the patients

Variables	Patients ($n=84$)
Age, mean ± SD (years)	66.8 ± 8.5
Sex	
Male/female	70/14
BMI, mean ± SD	20.9 ± 3.4
Tumor site	
Ut/Mt/Lt	14/32/38
cT	
1/2/3/4	1/2/80/1
cN	
1/2	62/22
cStage	
IIIA/IIIB/IIIC	64/19/1
NAC (yes/no)	77/7
Preoperative CRP, median (range) (mg/dl)	0.15 (0.10–2.66)
Preoperative Alb, mean ± SD (g/dl)	3.8 ± 0.5
Postoperative CRP, median (range) (mg/dl)	1.47 (0.13–7.86)
Postoperative Alb, mean ± SD (g/dl)	2.5 ± 0.5
ASA-PS (1/2/3/4)	26/44/13/1
Surgical approach	
Thoracoscopic approach	76
Thoracotomy[†]	8
Organ for reconstruction (gastric/ileocolon/jejunum)[‡]	73/4/5
Residual tumor (0/1)	74/10
Blood loss, median (range) (ml)	456 (30–2605)
Blood transfusion volume, median (range) (ml)	0 (0–2280)
Operation duration, median (range) (h)	11.6 (7.1–22.4)
All complications[§]	27
Respiratory complications	15
Digestive complications	9
Other complications	6

BMI body mass index, *Ut* upper thoracic, *Mt* middle thoracic, *Lt* lower thoracic, *cT* clinical T category, *cN* clinical N category, *NAC* neoadjuvant chemotherapy, *CRP* C-reactive protein, *Alb* albumin, *ASA-PS* American Society of Anesthesiologists-Physical Status, *SD* standard deviation

[†]Including two patients who were converted from a thoracoscopic approach

[‡]One patient did not undergo reconstruction

[§]Some cases overlapped

1.47 (0.13–7.86) mg/dl, respectively. The mean preoperative and postoperative Alb levels were 3.8 ± 0.5 and 2.5 ± 0.5 g/dl, respectively. The majority of the patients underwent thoracoscopic surgery, and two were converted to transthoracic approach. R0 resection was achieved in 74 patients (88.1%). The median (range) blood loss and operation duration were 456 (30–2605) ml and 11.6 (7.1–22.4) h, respectively. Blood transfusion was performed in 34 patients, and the median (range) blood transfusion volume was 0 (0–2280) ml. Complications over grade III in severity were observed in 27 patients, including 15 respiratory complications and 9 digestive complications.

According to an ROC analysis of the survival status, the optimum cut-off level for the preoperative CRP level was 0.15 mg/dl, with an area under the curve (AUC) of 0.660; the optimum cut-off level for the preoperative Alb level was 4.0 g/dl, with an AUC of 0.574; the optimum cut-off level for the postoperative CRP level was 2.44 mg/dl, with an AUC of 0.576; and the optimum cut-off level for the postoperative Alb level was 2.9 g/dl, with an AUC of 0.558.

Forty-six patients (54.8%) died during the observation period. Among those who died, 39 (84.8%) died within 3 years. The 3-year overall survival was 52.4% (Fig. 2). The survival was significantly higher when the preoperative CRP was < 0.15 mg/dl than when it was ≥ 0.15 mg/dl ($P=0.009$, Fig. 3). Univariate and multivariate analyses were performed

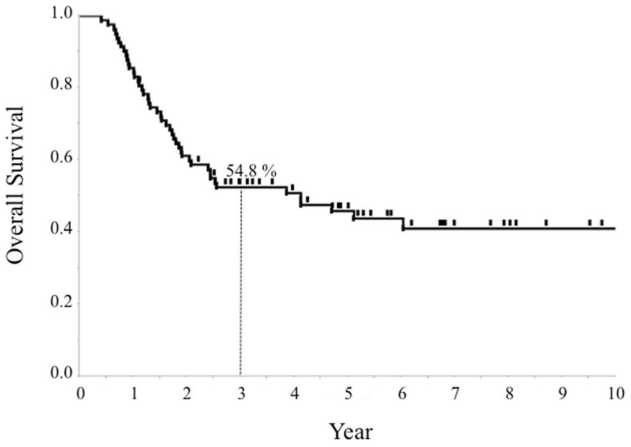

Fig. 2 The survival curve of cStage III esophageal cancer. The 3-year survival rate was 54.8%

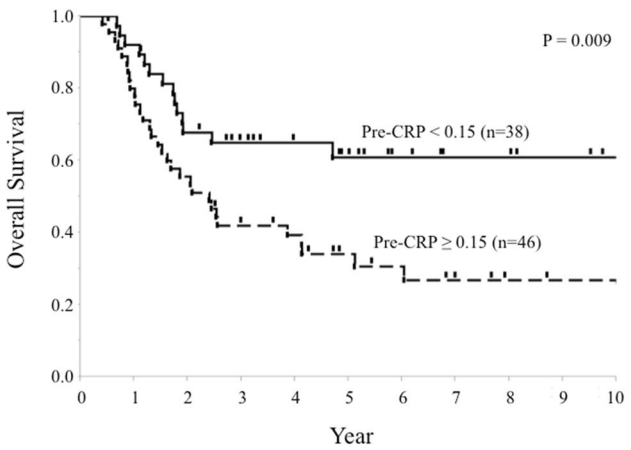

Fig. 3 Preoperative CRP < 0.15 had a higher survival rate than preoperative CRP ≥ 015

Table 2 Results of the analysis of the overall survival

Variables	Patients ($n=84$)	Univariate analysis		Multivariate analysis	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age, years (< 70)	49	0.856 (0.476–1.558)	0.606		
Sex (male)	70	1.571 (0.716–4.135)	0.278		
Tumor site (Mt, Lt)	70	1.227 (0.583–3.003)	0.612		
cT (1–3)	83	0.564 (0.122–10.023)	0.605		
cN (1)	62	1.359 (0.699–2.898)	0.379		
NAC	77	1.828 (0.653–7.659)	0.279		
Preoperative CRP (< 0.15)	38	0.443 (0.228–0.816)	0.009	0.435 (0.204–0.875)	0.019
Preoperative Alb (≥ 4.0)	37	0.684 (0.370–1.235)	0.209		
Postoperative CRP (< 2.44)	62	0.443 (0.244–0.828)	0.012	1.069 (0.449–2.567)	0.880
Postoperative Alb (≥ 2.9)	17	1.869 (0.945–3.487)	0.071	2.331 (1.122–4.654)	0.024
ASA-PS (≤ 2)	70	1.180 (0.538–3.105)	0.701		
Blood loss (< 600 ml)	57	0.386 (0.215–0.696)	0.002	0.478 (0.237–0.966)	0.040
Blood transfusion	34	1.627 (0.905–2.910)	0.103	0.792 (0.392–1.591)	0.513
Operation duration (< 12 h)	48	0.473 (0.260–0.846)	0.012	0.549 (0.256–1.181)	0.124
R0 resection	74	0.575 (0.273–1.409)	0.208		
All complications (< Grade 3)	57	0.390 (0.216–0.709)	0.002	0.433 (0.232–0.815)	0.010

HR, hazard ratio; CI, confidence interval; upper thoracic; Mt, middle thoracic; Lt, lower thoracic; cT, clinical T category; cN, clinical N category, NAC, neoadjuvant chemotherapy; POD, postoperative day; CRP, C-reactive protein; Alb, albumin; ASA-PS, American Society of Anesthesiologists-Physical Status

to determine the prognostic factors (Table 2). In the univariate analysis, preoperative CRP levels, postoperative CRP levels, blood loss, operation time, and complications were found to be prognostic factors ($P=0.009$, $P=0.012$, $P=0.002$, $P=0.012$, and $P=0.002$, respectively). In the multivariate analysis, preoperative CRP levels, postoperative Alb levels, blood loss, and complications were shown to be independent prognostic factors ($P=0.019$, $P=0.024$, $P=0.040$, and $P=0.010$, respectively).

The operation duration and preoperative CRP levels were significant factors affecting the postoperative CRP levels according to the multiple linear regression analysis (Table 3). There were no other significant factors affecting the postoperative CRP levels.

Table 3 Results of a multiple linear regression analysis of the variables affecting the postoperative CRP levels

Variables	Standardized coefficient	*P* value
Age, years	0.64	0.522
BMI	1.24	0.221
cT	0.13	0.894
cN	1.22	0.228
NAC	−0.33	0.740
Preoperative CRP	3.18	0.002
Preoperative Alb	−1.11	0.272
Postoperative Alb	1.78	0.079
ASA-PS	−1.97	0.053
Thoracoscopic approach	1.62	0.109
Gastric tube reconstruction	0.36	0.718
Blood loss	0.66	0.509
Blood transfusion	−0.28	0.783
Operation time	7.85	< 0.001

BMI body mass index, *ASA-PS* American Society of Anesthesiologists-Physical Status, *cT* clinical T category, *cN* clinical N category, *NAC* neoadjuvant chemotherapy, *CRP* C-reactive protein, *Alb* albumin

$R^2=0.67$

Discussion

Our study showed that the preoperative CRP levels were a significant prognostic factor, while the postoperative CRP levels were not. The preoperative CRP levels are affected by the tumor size, lymph node metastasis, and lymphatic invasion [11]. In contrast, the postoperative CRP levels are affected by surgical stress and postoperative complications [10, 13, 14]. In this study, we only assessed the postoperative CRP levels just after the operation to exclude the effect of postoperative complications. Therefore, the prognosis of esophageal cancer might be more strikingly affected by the preoperative status than surgical stress. We also previously showed that the CRP and Alb values around and after NAC reflect the prognosis better than those values before NAC [9, 19]. This suggests that managing the preoperative status is important for improving the prognosis.

The postoperative CRP levels measured just after the operation were significantly affected by the operation duration. The CRP level measured on POD 1 was also affected by the operation duration; however, the CRP level measured just after the operation had a stronger relationship with the operation duration than that measured at POD 1 (data not shown). The relationship between the CRP levels and the operation duration might be due to surgical stress. Surgical stress induces the production of proinflammatory cytokines, such as interleukin (IL) and tumor necrosis factor-α [3–7]. These cytokines lead to acute lung injury and multiple organ dysfunction [20]. Okamura et al. showed that there was a significant correlation between increased levels of IL-6 and the operation duration [3]. Since CRP is known to release inflammatory cytokines and induce the shedding the IL-6 receptor [21, 22], there also maybe a correlation between the postoperative CRP levels and the operation duration, as observed in our study.

Improvements in the operation method and the use of anti-inflammatory drugs have been attempted in order to reduce the postoperative cytokine levels, to some success. Thoracoscopic surgery is known to have equivalent short- and long-term operative outcomes [23, 24] but lower cytokine levels than thoracotomy [3, 25]. Using anti-inflammatory drugs successfully suppressed the cytokine levels without increasing the rate of adverse outcomes [7, 20, 26, 27]. However, most of these reports described only the short-term outcomes, and the long-term outcomes remain unclear. Given concerns that immunosuppression might increase the recurrence rate [28], further studies will be needed to clarify whether or not anti-inflammatory drugs can be safely used in general practice.

Several limitations associated with the present study warrant mention. First, the operative procedure varied among patients, which might have affected the postoperative CRP levels. Second, this was a retrospective study conducted at a single institution with a small sample size. Further multicenter, large-scale studies will be required to confirm our findings.

In conclusion, the preoperative CRP levels, postoperative Alb levels, and complications were shown to be independent prognostic factors for cStage III esophageal cancer. Furthermore, the postoperative CRP levels were significantly affected by the operation duration and preoperative CRP levels. Therefore, preoperative treatment might help improve the preoperative CRP levels, and reducing the operation duration might reduce the inflammatory response, which might help improve the survival of cStage III esophageal cancer.

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Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to declare.

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