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ORIGINAL ARTICLE – THORACIC ONCOLOGY

Factors Affecting Cytokine Change After Esophagectomy for Esophageal Cancer

Akihiko Okamura, MD[1], Hiroya Takeuchi, MD, PhD[1], Satoru Matsuda, MD[1], Masaharu Ogura, MD, PhD[1], Taku Miyasho, PhD[2], Rieko Nakamura, MD, PhD[1], Tsunehiro Takahashi, MD, PhD[1], Norihito Wada, MD, PhD[1], Hirofumi Kawakubo, MD, PhD[1], Yoshiro Saikawa, MD, PhD[1], and Yuko Kitagawa, MD, PhD[1]

[1]Department of Surgery, School of Medicine, Keio University, Tokyo, Japan; [2]School of Veterinary Medicine, Rakuno Gakuen University, Hokkaido, Japan

ABSTRACT

Background. Esophagectomy for esophageal cancer is one of the most invasive operative procedures. Surgical stress induces the release of proinflammatory cytokines, and overproduction induces a systemic inflammatory response syndrome, which may lead to acute lung injury and multiple organ dysfunction syndrome. In addition, surgical stress may cause immunosuppression, which may affect not only perioperative mortality but also long-term survival.

Methods. Between 2006 and 2013, levels of perioperative serum cytokines were evaluated in 90 patients who underwent esophagectomy for esophageal carcinoma. The serum interleukin (IL)-6, IL-8, and IL-10 levels were measured by enzyme-linked immunosorbent assays. We reviewed and assessed medical records, including cytokine profiles, and determined the factors affecting postoperative serum cytokine levels.

Results. These cytokine levels peaked on postoperative day 1 and decreased gradually. Of the clinicopathologic factors, a thoracoscopic approach was a significant factor in attenuating IL-6 and IL-8 levels on postoperative day 1 in multivariate analysis, and a longer operative time was a significant factor in increasing these levels. During postoperative days 3–7, the thoracoscopic approach and early enteral nutrition were significant factors in attenuating serum cytokine changes in multivariate analysis, and postoperative infectious complications were significant factors in increasing these levels.

Conclusions. The thoracoscopic approach and early enteral nutrition could attenuate the cytokine change after esophagectomy, and a longer operative time and postoperative infectious complication could increase it. We should undertake strategies to minimize the surgical stress to reduce potential short-term and long-term consequences for patients.

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H. Takeuchi, MD, PhD
e-mail: htakeuchi@a6.keio.jp

Radical esophagectomy for esophageal cancer is one of the most invasive operative procedures. Despite advances in surgical techniques and postoperative management, postoperative complications often occur.[1] Surgical stress induces the release of proinflammatory cytokines, and the overproduction of these cytokines also induces a systemic inflammatory response syndrome (SIRS), which may lead to acute lung injury and multiple organ dysfunction syndrome.[2] In addition, surgical stress could cause immunosuppression in response to the complex interaction of various hormones, cytokines, and acute phase reactants.[3] It has been reported that perioperative immunosuppression increased the incidence of cancer recurrence and reduced survival.[4–6] Therefore, the development of effective measures against the overproduction of proinflammatory cytokines, postoperative complications, and immunosuppression is expected. Less invasive esophagectomy procedures and some drugs that could attenuate surgical stress have been developed and investigated.[1,2,7–23] With this background, thoracoscopic esophagectomy (TE) is being increasingly implemented as a less invasive treatment.

We hypothesized that some clinicopathologic factors could be related to the attenuation of the cytokine change after esophagectomy. In this study, we reviewed the patients who underwent radical esophagectomy for esophageal cancer and could be evaluated for levels of perioperative serum cytokines, which were collected prospectively. We assessed their perioperative data, including cytokine profiles, and determined the factors that affected postoperative serum cytokine levels.

PATIENTS AND METHODS

Patients

Between 2008 and 2013, there were 90 patients who underwent radical esophagectomy for primary esophageal cancer that could be evaluated for perioperative serum cytokines levels until postoperative day (POD) 7 at the Department of Surgery, Keio University Hospital, Tokyo, Japan. These patients constituted our study population and had undergone routine preoperative evaluations including blood examinations, esophagogastroduodenoscopy with biopsy, computed tomography, barium swallow, electrocardiography, spirometry, and indocyanine green retention rate test. All the patients were assessed for their ability to tolerate general anesthesia and major surgical stress. We reviewed the medical records, assessed their clinicopathologic data including cytokine profiles, and determined the factors affecting postoperative serum cytokine levels. The tumor stage was defined as the pathologic stage and was classified according to the 7th edition of the tumor, node, metastasis classification system of the Union for International Cancer Control.[24] The definition of postoperative complications was those issues that required pharmacologic treatment with drugs, at least, which were classified as more than a grade II complication in the Clavien–Dindo classification.[25] The definition of SIRS was taken from the report by the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference.[26] This protocol was approved by the institutional review board of Keio University Hospital.

Surgical Procedures

During this period, 25 patients underwent conventional open transthoracic esophagectomy (OE) and 65 patients underwent TE. None of the patients who underwent TE was converted to OE. In the patients who underwent OE, the thoracic procedure was performed through a right thoracotomy with two- or three-field lymphadenectomy in the left lateral decubitus position. In the patients who underwent TE, the thoracic procedure was performed in a hybrid position combining the left lateral decubitus and prone positions. This position took advantage of both the left lateral decubitus and prone positions, as we had reported previously.[19] In both the groups, either a cervical or intrathoracic anastomosis was performed depending on the tumor location. In the patients who received early enteral nutrition with the physicians' choice, a jejunostomy catheter was also placed. Early enteral nutrition was started using a small amount of elemental nutrition after esophagectomy immediately, and the dose was gradually increased.

Postoperative Management

During this period, there was no change in the management of postoperative care, including respiratory care and administered drugs that could attenuate perioperative serum cytokine levels. Hydrocortisone sodium phosphate was administered at a dosage of 200 mg per day, from preoperative day 2 until POD 3. In addition, the neutrophil elastase inhibitor, sivelestat, was also administered to all the patients after esophagectomy. All the patients were routinely admitted to the intensive care unit on mechanical ventilation at least overnight after esophagectomy. The patients were extubated on POD 1 and were discharged from the intensive care unit on the day after extubation, if their condition was stable.

Measurements

Blood samples were collected, centrifuged, and stored at −80 °C. The serum cytokine, such as interleukin (IL)-6, IL-8 and IL-10, level were measured at five points (preoperatively and on PODs 1, 3, 5, and 7), by enzyme-linked immunosorbent assay (School of Veterinary Medicine, Rakuno Gakuen University, Hokkaido).

Statistical Analysis

The data were analyzed as the mean ± standard deviation. Statistical analyses were performed by the SPSS software package, version 22.0 (IBM, Armonk, NY). Correlation analysis was performed by Spearman's rank correlation coefficient analysis. Multivariate analysis was performed by multiple linear regression analysis. A probability level of 0.05 was chosen for statistical significance.

RESULTS

Patient Characteristics and Surgical Outcomes

Patients' characteristics and surgical outcomes are summarized in Table 1. Of the 90 patients, 53 (59 %) were treated with neoadjuvant chemotherapy before the surgery, 6 (7 %) of whom also received radiotherapy. Eight patients (9 %) were treated with endoscopic resection before the surgery, and 29 patients (32 %) received no preoperative treatment. Twenty-five patients (28 %) underwent OE, and 65 patients (72 %) underwent TE. Fifty patients (55 %)

TABLE 1 Patient characteristics and surgical outcomes

Characteristic	Variable	Value
Age (years)		63.9 ± 9.1
Sex	Male	79 (87)
	Female	11 (13)
Neoadjuvant chemotherapy	Yes	53 (59)
	No	37 (41)
Histology	Squamous cell carcinoma	82 (91)
	Other	8 (9)
Main tumor location	Cervical and upper thoracic	12 (13)
	Middle thoracic	46 (51)
	Lower and abdominal	32 (36)
pT category	pT ≤ 1b	49 (55)
	pT ≥ 2	41 (45)
pN category	pN0	41 (45)
	pN ≥ 1	49 (55)
pStage category	pStage ≤ II	56 (62)
	pStage ≥ III	34 (38)
Surgical approach	Open transthoracic	25 (28)
	Thoracoscopic	65 (72)
Extent of lymphadenectomy	Two-field	28 (32)
	Three-field	62 (68)
Early enteral nutrition	Yes	50 (55)
	No	40 (45)
Operation time (min)		551.2 ± 86.2
Operative blood loss (mL)		302.1 ± 499.9
Infectious complication	All	43 (47)
	Pneumonia	23 (25)
	Anastomotic leakage	23 (25)

Data are provided as mean ± SD or *n* (%)

underwent the placement of a jejunostomy catheter and received early enteral nutrition. Forty-three patients (47 %) had postoperative infectious complications, which were diagnosed by clinical and radiologic examinations. Among them, 23 patients (25 %) had pneumonia and 23 patients (25 %) had anastomotic leakage. None of the patients died of postoperative complications within 30 days after the surgery.

Perioperative Changes in Serum Cytokine Levels

We evaluated the perioperative changes in serum IL-6, IL-8, and IL-10 levels. These cytokine levels peaked on POD 1. The mean IL-6 level on POD 1 was 182.1 ± 197.7 pg/mL, that of IL-8 was 26.8 ± 18.9 pg/mL, and that of IL-10 was 26.2 ± 114.9 pg/mL. These cytokine levels gradually decreased after the peak (Fig. 1).

Correlation Between Serum Cytokine Levels and Duration of SIRS After Esophagectomy

We evaluated the correlation between serum cytokine levels on POD 1 and the duration of SIRS after esophagectomy. Spearman's rank correlation coefficient analysis revealed a significant correlation between the serum IL-6 level on POD 1 and the duration of SIRS after esophagectomy ($r_s = 0.38$, $p < 0.01$). In addition, there was a significant correlation between the serum IL-8 level on POD 1 and the duration of SIRS after esophagectomy ($r_s = 0.35$, $p < 0.01$) in this analysis. However, there was no correlation between the serum IL-10 level on POD 1 and the duration of SIRS after esophagectomy.

Factors Affecting Serum Cytokine Levels on POD 1

Of the clinicopathologic factors, the thoracoscopic approach and operation time were significant factors affecting the serum cytokine levels on POD 1 in the multiple linear regression analysis (Table 2). The thoracoscopic approach attenuated the levels of serum IL-6 (standardized coefficient = −0.36, $p = 0.01$) and IL-8 (standardized coefficient = −0.45, $p < 0.01$) on POD 1. On the other hand, longer operative time increased the levels of these cytokines (IL-6: standardized coefficient = 0.43, $p < 0.01$, IL-8: standardized coefficient = 0.28, $p = 0.01$). Although, early enteral nutrition was not a significant factor, there was a trend toward attenuation of the levels of the serum IL-8 on POD 1 (standardized coefficient = −0.22, $p = 0.07$). Age, neoadjuvant chemotherapy, tumor stage, operative blood loss, and infectious complication were not significant factors affecting the serum IL-6 and IL-8 levels on POD 1. There were no significant factors affecting serum IL-10 levels on POD 1 (data not shown).

Factors Affecting Serum Cytokine Levels during PODs 3–7

During PODs 3–7, the thoracoscopic approach, early enteral nutrition, and postoperative infectious complications were significant factors affecting the serum cytokine changes in the multiple linear regression analysis (Table 3). The thoracoscopic approach attenuated the levels of serum IL-6 on POD 7 (standardized coefficient = −0.29, $p = 0.04$), and IL-8 on PODs 3, 5, and 7 (POD 3: standardized coefficient = −0.41, $p < 0.01$, POD 5: standardized coefficient = −0.28, $p = 0.04$, POD 7: standardized coefficient = −0.36, $p = 0.01$). Early enteral nutrition attenuated the levels of serum IL-8 on POD 3 (standardized coefficient = −0.29, $p = 0.02$). In addition, the influences due to postoperative infectious complications such as pneumonia and anastomotic leakage were also seen during this period. Postoperative infectious

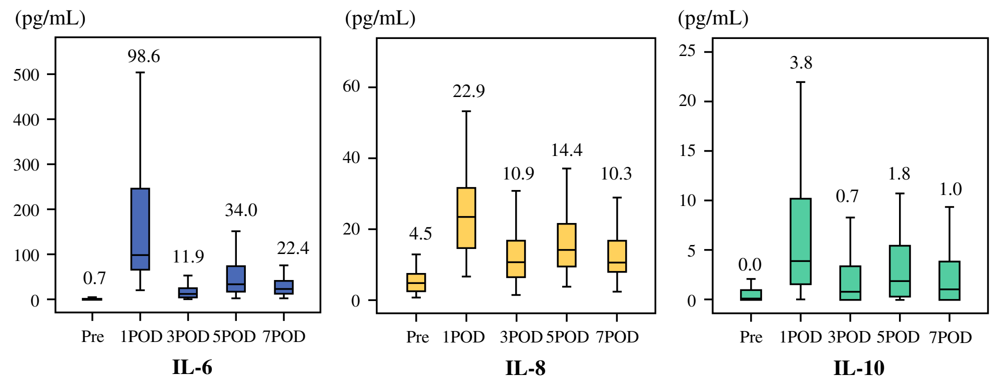

FIG. 1 Perioperative changes in serum cytokine levels. The median serum levels of IL-6, IL-8, and IL-10 at each time point are indicated by the *horizontal bars*, and each median value is represented. Outliers are not represented. *Vertical bars* indicate range, except for outliers, and the *horizontal boundaries* of the *boxes* represent the first and third quartiles

TABLE 2 Multiple linear regression analysis of the factors affecting the serum cytokine levels on postoperative day 1

Factor	IL-6		IL-8	
	Standardized coefficient	*p*	Standardized coefficient	*p*
Age (years)	0.12	0.23	0.06	0.55
Neoadjuvant chemotherapy	0.13	0.27	0.04	0.70
pStage ≥ III	−0.07	0.50	0.04	0.69
Thoracoscopic approach	−0.36	0.01*	−0.45	<0.01*
Operation time (min)	0.43	<0.01*	0.28	0.01*
Operative blood loss (mL)	0.00	0.98	−0.09	0.37
Early enteral nutrition	−0.14	0.23	−0.22	0.07†
Infectious complication	−0.05	0.63	0.10	0.31
	$R^2 = 0.21$		$R^2 = 0.17$	

* $p < 0.05$, † $p < 0.10$ (multiple linear regression analysis)

complications increased the levels of serum IL-6 on POD 5 (standardized coefficient = 0.23, $p = 0.03$), and IL-8 on PODs 3 and 5 (POD 3: standardized coefficient = 0.24, $p = 0.02$, POD 5: standardized coefficient = 0.27, $p = 0.01$). Age, neoadjuvant chemotherapy, tumor stage, operation time, and operative blood loss were not significant factors, and there were no significant factors affecting serum IL-10 levels during PODs 3–7 (data not shown).

DISCUSSION

The present study led to two major findings. First, the thoracoscopic approach and early enteral nutrition could attenuate the cytokine change after esophagectomy for esophageal cancer. Second, a longer operative time and postoperative infectious complications such as pneumonia or anastomotic leakage could increase this change.

Major invasive surgery including esophagectomy causes the release of proinflammatory cytokines. The ability to mount an appropriate inflammatory response serves to restore homeostasis to the injured patient.[27] However, this requires the simultaneous influences of SIRS, the compensatory anti-inflammatory response syndrome, and the disruption of this balance toward either extremes can precipitate immunosuppression, cardiovascular collapse, and organ dysfunction.[28] It has been suggested that such immunosuppression was associated with impaired wound healing, postoperative infectious complications, increased incidence of cancer recurrence, and reduced survival.[4–6,29,30] We had previously reported that postoperative infectious complications affected not only perioperative mortality but also the long-term survival of the patients undergoing esophagectomy after definitive chemoradiation.[31] Therefore, efforts focused on minimizing the systemic inflammatory response after esophagectomy should be made.

In the present study, we also showed that there were positive and significant correlations between serum IL-6 and IL-8 levels on POD 1 and the duration of SIRS after esophagectomy. The duration of postoperative SIRS could be predicted by measurements of serum cytokine levels on POD 1. It was also suggested that the reduction of postoperative serum cytokine levels could shorten the duration of SIRS after esophagectomy. Attenuating the cytokine change might be expected to reduce not only the patients' outcomes but also their loads after esophagectomy.

To limit surgical trauma and to attenuate surgical stress, less invasive esophagectomy procedures have been developed and investigated.[1,7,11–17,19,21–23] Regarding the thoracoscopic approach, in 1992, Cuschieri et al. first reported on TE and more evidence about TE has been collected.[7] Acceptable short-term outcomes of TE that are

TABLE 3 Multiple linear regression analysis of the factors affecting the serum cytokine levels during PODs 3–7

Factor	*p* values for IL-6 on			*p* values for IL-8 on		
	POD 3	POD 5	POD 7	POD 3	POD 5	POD 7
Age (years)	0.84	0.69	0.57	0.37	0.92	0.42
Neoadjuvant chemotherapy	0.65	0.43	0.86	0.06	0.83	0.13
pStage ≥ III	0.43	0.29	0.20	0.40	0.62	0.96
Thoracoscopic approach	0.29	0.15	0.04*	<0.01*	0.04*	0.01*
Operation time (min)	0.77	0.26	0.93	0.24	0.64	0.06
Operative blood loss (mL)	0.93	0.64	0.74	0.55	0.35	0.59
Early enteral nutrition	0.70	0.85	0.64	0.02*	0.65	0.66
Infectious complication	0.38	0.03*	0.96	0.02*	0.01*	0.72

POD postoperative day

* $p < 0.05$ (multiple linear regression analysis)

comparable to OE have been reported.[21] Biere et al. first reported a multicenter, open-label, randomized controlled trial to compare TE and OE.[1] The incidence of pulmonary infectious complications was markedly lower in the TE group than in the OE group. Additional benefits of TE included less operative blood loss, better postoperative patient quality of life, and shorter hospital stays.

From the aspect of postoperative cytokine change, Tsujimoto et al. reported that TE induced significantly lower levels of postoperative IL-6, IL-10, and IL-18 compared with OE.[16] In the present study, our TE was the significant factor attenuating postoperative IL-6 and IL-8 levels in multivariate analysis. We had previously reported that our TE procedure performed in a hybrid position could attenuate the severity of intraoperative pulmonary damage while facilitating a more radical mediastinal lymphadenectomy. Thus, we believe that the thoracoscopic approach could be a less invasive approach that attenuates the cytokine change after esophagectomy.

We demonstrated that a longer operative time and postoperative infectious complications could increase the cytokine change after esophagectomy. Haga et al. reported that the duration of SIRS or the positive criteria number of SIRS after gastrointestinal surgery correlated with operation time.[32] In addition, it was reported that the patients with acute lung injury or pneumonia had higher levels of serum IL-6 after esophagectomy than those without acute lung injury or pneumonia.[33,34] Our results were consistent with these reports. It was also suggested that the early elevation of postoperative cytokine levels may predict the incidence of the postoperative infectious complication.[34]

Early enteral nutrition is preferred over parenteral nutrition for patients undergoing esophagectomy. It has been reported that early enteral nutrition after esophagectomy ameliorated the postoperative nutritional status of these patients, preserved the intestinal mucosa's integrity and immunologic functioning, and reduced the incidences of postoperative infectious complications.[35–38] Takagi et al. reported that perioperative enteral nutrition attenuated the levels of serum IL-6 on PODs 3 and 7 in the patients who underwent esophagectomy.[39] They also reported that enteral nutrition significantly attenuated postoperative levels of serum endotoxin. Kotani et al. reported that enteral nutrition prevented bacterial and endotoxin translocation in a severe acute pancreatitis rat model.[40] In our study, early enteral nutrition was a significant factor attenuating levels of serum IL-8 on POD 3. It was suggested that early enteral nutrition had some modulating effects on the cytokine change after esophagectomy. These effects of enteral nutrition could lower the possibility of infectious complications.

In conclusion, understanding the factors affecting the cytokine change after esophagectomy, we should undertake strategies that minimize surgical stress to reduce potential short-term and long-term consequences for patients. The thoracoscopic approach and early enteral nutrition could attenuate the cytokine change after esophagectomy for esophageal cancer. In addition, efforts focused on shortening the operation time and reducing postoperative complications should be made.

DISCLOSURE The authors declare no conflict of interest.

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