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Intraoperative Blood Transfusion Contributes to Decreased Long-Term Survival of Patients With Esophageal Cancer

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Abstract

Background Several prognostic factors for patients who have undergone esophagectomy owing to esophageal squamous cell carcinoma have been suggested, including intraoperative blood loss. There are few data, however, suggesting such an association with the prognosis following radical esophagectomy.

Methods Patients with esophageal squamous cell carcinoma who underwent radical esophagectomy were divided into two groups based on the median value of the intraoperative blood loss (510 g). A multivariate Cox proportional-hazard regression analysis was performed to determine if intraoperative blood loss could be an independent prognostic factor for long-term survival following radical esophagectomy. Kaplan–Meier survival analysis with a log-rank test was performed between the groups.

Results From April 2005 to May 2009, a total of 37 patients underwent radical esophagectomy for the treatment of esophageal squamous cell carcinoma at the Juntendo Shizuoka Hospital and were assigned either to one of two groups: those with ≥510 g blood loss [bleeding group (BG), $n = 19$] or of those with <510 g blood loss [less bleeding group (LBG), $n = 18$]. The distribution of the stage of disease, the number of positive lymph nodes, and the presence of lymphatic and vascular invasion was comparable between the groups, but the Kaplan–Meier survival analysis demonstrated that survival was significantly worse in the BG group than in the LBG group ($p = 0.00295$). This was supported by the multivariate analysis, which indicated that intraoperative blood loss was independently associated with long-term survival after radical esophagectomy.

Conclusions Intraoperative blood loss could be a useful prognostic factor following radical esophagectomy in patients with esophageal squamous cell carcinoma.

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Introduction

Worldwide, esophageal cancer has been a significantly increasing health problem, being the seventh leading cause of cancer-related death. In 2005, there were approximately 500,000 new cases, and the prevalence is expected to increase by approximately 140% by 2025 [1]. Squamous cell carcinoma (SCC) is responsible for more than 90% of all esophageal cancers worldwide, as it is in Japan [2]. In Western countries, however, adenocarcinoma has exceeded SCC over the past few decades and become the most prevalent form of esophageal cancer [2, 3].

Treatment options for esophageal cancer including the surgical approach, extent of lymphadenectomy, and chemotherapy and radiation therapy have been tailored based on the individual staging, tumor biology and medical comorbidities. In the West, a transhiatal or transthoracic esophagectomy with limited lymph node dissection has played a major role in the multidisciplinary treatment of resectable esophageal adenocarcinoma [2]. However, in Japan, as a standard of surgical approach, an extended transthoracic esophagectomy with three-field lymphadenectomy

has been performed since the 1980s and has been demonstrated to contribute to improved long-term survival of patients with esophageal SCC [4]. Currently, the standard of care for resectable esophageal SCC in Japan is neoadjuvant chemotherapy with 5-fluorouracil/cisplatin followed by an extended intrathoracic esophagectomy with three-field lymphadenectomy [5, 6].

The following factors have been reported to be associated with overall survival in patients with esophageal SCC: age, sex, tumor size, tumor depth, tumor location, tumor stage at the time of presentation, blood vessel invasion, neural invasion, lymph node status, number of positive lymph nodes, resection margins, type of resection, red blood cell transfusion, operating time, and adjuvant chemotherapy [4, 7–10]. Intraoperative blood loss and red blood cell transfusion have been reported as prognostic factors for other types of cancer, such as colorectal cancer, gastric cancer, hepatocellular carcinoma, ductal adenocarcinoma of the pancreas, and prostate cancer [11–15]. Although several studies have examined the impact of blood transfusion on prognosis [16, 17], there are few studies demonstrating the association between the amount of intraoperative blood loss and the long-term outcome of patients with esophageal SCC following radical esophagectomy. The aim of this study was to determine retrospectively the independent prognostic factors, especially intraoperative factors such as blood loss, after curative resection of esophageal SCC.

Methods

Study design and patient selection

This retrospective review of prospectively collected data was performed with the approval of our institutional review board at the Juntendo Shizuoka Hospital. Eligible subjects included patients with esophageal SCC who underwent radical esophagectomy with three-field lymphadenectomy between April 2005 and May 2009 regardless of neoadjuvant or adjuvant chemotherapy and/or radiation therapy. The patient's demographic data and procedure data were obtained either from the medical records or a phone interview with patients. Patients who met any of the following criteria were excluded from this study: presence of other coexisting carcinomas, postoperative mortality within 90 days, any pathologic type other than squamous cell carcinoma, presence of distant metastases at the time of the preoperative workup. The patients were divided into two groups based on the median value of the intraoperative blood loss (510 g): bleeding group (BG, ≥510 g) and less-bleeding group (LBG, <510 g).

Clinicopathologic variables

As candidates of prognostic factors for long-term survival after radical esophagectomy, the following clinicopathologic variables were chosen for the univariate and multivariate analyses: intraoperative blood loss, age, sex, tumor location, tumor size, stage of disease, positive lymph nodes, blood transfusion, adjuvant chemotherapy and radiation therapy, lymphatic invasion, vascular invasion. Intraoperative blood loss was calculated at the end of each case by adding the weight of contents in the suction containers to the weight of surgical sponges used during the surgery. Tumor size was defined as the maximum diameter of the tumor, which was obtained from the pathology reports. Lymphovascular invasion was considered present when the presence of tumor cells within lymphatics and vessels was confirmed microscopically. The final pathological staging was determined using the 2002 staging system of the International Union against Cancer (UICC).

Statistical analysis

Data were expressed as a mean ± standard deviation where appropriate. Comparison (univariate analysis) between the groups was performed using the standard X^2 test and the Mann–Whitney U-test where appropriate. Survival at 3 years was calculated via the Kaplan–Meier method, and a statistical analysis was carried out using the log-rank test for equality of survival curves. To determine a possible independent prognostic factor, a multivariate analysis was performed using a Cox proportional hazards model. A p value <0.05 was considered to indicate a statistically significant difference with a 95% confidence interval (95% CI). Model X^2 test was used to evaluate the compatibility of this analysis. All statistical analyses were performed using SPSS (version 16.0; SPSS Japan, Tokyo, Japan).

Results

Between April 2005 and May 2009, a total of 43 patients with SCC underwent radical esophagectomy. All patients had complete macroscopic resection of their disease, and SCC was confirmed histopathologically in all patients. There was no obvious evidence of metastatic disease in any of these patients. Most of the patients ($n = 41$) underwent a right transthoracic subtotal esophagectomy with three-field lymphadenectomy including cervical (bilateral supraclavicular regions), mediastinal (paraesophageal and tracheal regions, including the bilateral recurrent laryngeal nerves), and abdominal (perigastric region and around the celiac axis) lymph nodes followed by reconstruction with

either stomach ($n = 39$) or jejunum ($n = 2$) by the same surgeon (K.S.). Two patients with SCC of the cervical esophagus underwent esophagectomy in conjunction with laryngectomy followed by reconstruction with stomach; these two patients were included in this study. Four patients who died within 90 days after surgery were excluded to avoid the effects of surgery-related postoperative complications on long-term survival. Two patients with coexisting carcinoma were excluded. Hence, a total of 37 patients were enrolled in the study (Fig. 1). None of 37 patients received neoadjuvant chemotherapy. In all, 4 patients were given adjuvant chemotherapy, 1 patient was given adjuvant radiation therapy, and 20 patients underwent both adjuvant chemotherapy and radiation therapy. Cisplatin (60–80 mg/m^2, 1 day/week) and 5-fluorouracil (5-FU) (700–800 mg/m^2, 5 days/week) was the most commonly used regimen in these patients. Twelve patients did not receive any adjuvant treatment including four patients with superficial SCC, one patient who was >80 years of age, and seven patients who refused.

These 37 patients were then assigned to the BG group ($n = 19$) or the LBG group ($n = 18$) based on the criteria. Patient demographics and the clinicopathologic variables of each group are summarized in Table 1. The distribution of sex and age was comparable between the groups. The mean amount of blood loss in each group was 317 g (range 160–500 g) in the LBG group and 1017 g (range 510–2780 g) in the BG group. In 29% (11/37) of patients, blood transfusion with a median of 500 g (range 280–1650 g) was required. Only one patient in the LBG group, whose intraoperative blood loss was 500 g, required blood transfusion. The mean tumor size of all patients was
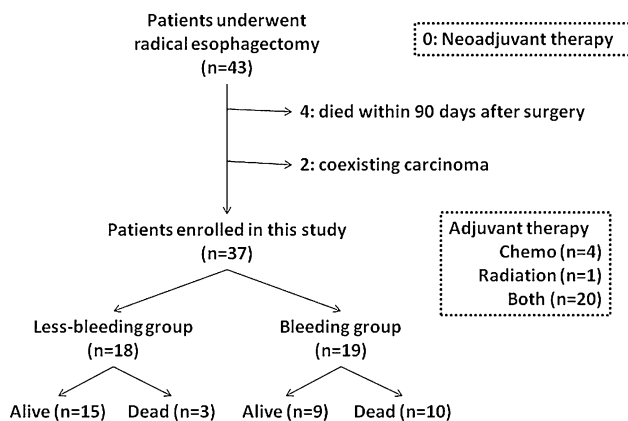

Fig. 1 A total of 43 patients underwent radical esophagectomy without neoadjuvant therapy. Four patients who died within 90 days and two patients with coexisting carcinoma were excluded. The remaining 37 patients were enrolled in this study and divided into two groups: less-bleeding group ($n = 18$) and bleeding group ($n = 19$). In all, 4 patients underwent chemotherapy, 1 patient underwent radiation therapy, and 20 patients underwent both chemotherapy and radiation therapy

Table 1 Clinicopathologic variables of the bleeding and less-bleeding groups

Variable	Bleeding group ($n = 19$)	Less-bleeding group ($n = 18$)	p
Intraoperative blood loss (g)	1017 ± 529 (range 510–2780)	317 ± 103 (range 160–500)	<0.0001*
Sex			
Male	17	16	0.956
Female	2	2	
Age (years)	66.6 ± 7.9 (range 53–81)	64.7 ± 8.5 (range 45–74)	0.48
Depth of tumor			
T1	4	2	0.405
T2	7	8	
T3, T4	8	8	
Positive nodes			
0	8	7	0.847
1–3	8	8	
≥4	3	3	
Lymphatic invasion			
Positive	17	18	0.166
Negative	2	0	
Vascular invasion			
Positive	16	12	0.229
Negative	3	6	
Tumor size (cm)	4.7 ± 2.3 (range 1.5–9.0)	5.3 ± 1.5 (range 2.5–9.0)	0.728
Stage of the disease			
I	4	3	0.955
II	7	6	
III	8	9	
Blood transfusion			
Required	10	1	0.009*
Not required	9	17	
Tumor location			
Cervical	2	1	0.842
Thoracic	16	16	
Abdominal	1	1	
Adjuvant therapy			
Chemotherapy	1	3	0.836
Irradiation	0	1	
Chemoirradiation	11	9	

Variables were expressed as a mean ± SD where appropriate

T1 tumor invades mucosal or submucosal layer only, *T2* tumor invades the muscularis propria, *T3* tumor invades adventitia, *T4* contiguous spread into surrounding structures

* Value of $p < 0.05$ was considered significant

5 cm (range 1.5–9.0 cm). However there was a trend that the tumor size in the LBG group was larger than that in the BG group (5.3 ± 1.5 vs. 4.7 ± 2.3 cm, respectively). In 32

Table 2 Mode of recurrence and metastasis of each group

Variable	Bleeding group	Less-bleeding group	p
Cervical LN recurrence	2	1	0.033
Bronchial LN recurrence	2	6	0.5
Bronchial LN recurrence and lung metastasis	2	1	0.033
Liver metastasis	2	0	0.011*
Total LN recurrence (cervical and bronchial)	4	7	0.147
Total remote metastasis (liver and lung)	4	1	0.147

LN lymph node

* A value of $p < 0.05$ was considered significant

Fig. 2 Survival curves for 19 patients in the bleeding group and 18 patients in the less-bleeding group. There was significant difference in survival between the two groups ($p = 0.00295$). Data were analyzed using a log-rank test

of 37 (86%) patients, the primary tumor was located in the thoracic esophagus. The amount of blood transfusion required was significantly higher in the BG group ($p = 0.009$), whereas depth of tumor, the number of positive nodes, tumor size, TNM staging, and the presence of lymphovascular invasion were comparable between the groups.

Most of the patients had a history of smoking and alcohol consumption. Postoperatively, pulmonary complications such as atelectasis, pleural effusion, and pneumonia were the most commonly observed (BG group, $n = 16$; LGB group, $n = 8$). Worsening pulmonary function was seen in three patients after recovery from the surgery (BG group, $n = 3$; LBG group, $n = 0$). These three patients had recovered well from surgery for a while, but their pulmonary function got worse several months after surgery because they developed interstitial pneumonia. Two of them required oxygen therapy. Stricture of an anastomosis was found in three patients (BG group, $n = 2$; LBG group, $n = 1$). No anastomotic leakage was reported.

During a mean follow-up of 48 months (range 4–60 months), lymph node recurrence and/or remote organ metastasis occurred in eight patients in the BG group [cervical lymph node ($n = 2$), bronchial lymph node ($n = 2$), liver metastasis ($n = 2$), and both bronchial lymph node and lung metastasis ($n = 2$)] and in eight patients in the LBG group [bronchial lymph node ($n = 6$), cervical lymph node ($n = 1$), and both bronchial lymph node and lung metastasis ($n = 1$)] (Table 2). There was a significant difference in the incidence of liver metastasis between the BG and LBG groups (2 vs. 0, $p = 0.011$), whereas there was no difference in the combined data of remote organ metastasis (liver and lung) between the groups (4 vs. 1, $p = 0.147$). There was no difference in the mode of lymph node recurrence between the groups. Among them, all eight patients in the BG group and three patients in the LBG group died of recurrent and/or
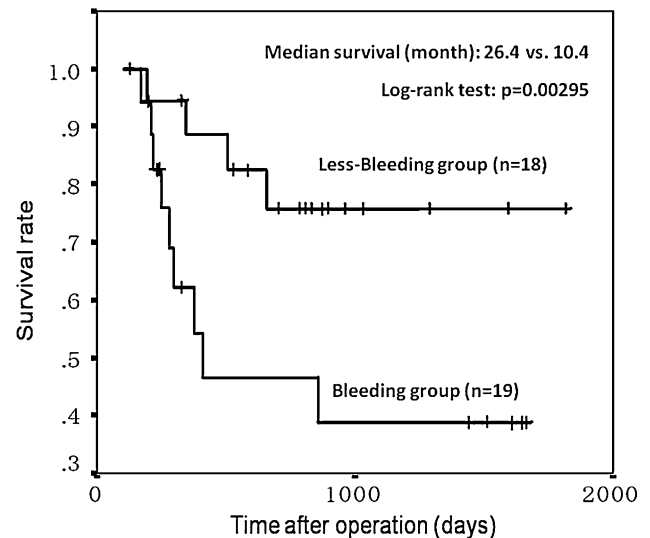
metastatic disease. On the other hand, two patients in the LBG group died of other underlying diseases such as liver cirrhosis and chronic obstructive lung disease. Eventually, a total of 13 patients died during the follow-up period for this study.

The median survival of patients in the BG group was significantly shorter than that of patients in the LBG group (10.4 vs. 26.4 months, respectively; $p = 0.00295$). The Kaplan–Meier analysis demonstrated that the survival was significantly worse in the BG group than in the LBG group. The 3-year survival rates for the BG and LBG groups were 37 and 77%, respectively (Fig. 2). This suggests that the amount of intraoperative blood loss is highly associated with survival after radical esophagectomy even though the distribution of the stage of disease, the number of positive lymph nodes, and presence of lymphovascular invasion are comparable between the groups.

To determine if the amount of intraoperative blood loss and/or other variables could be an independent prognostic factor, a multivariate analysis was performed (Table 3). Multivariate analysis demonstrated that the stage of the disease, positive lymph nodes, and blood transfusion in addition to intraoperative blood loss were independent prognostic factors ($p < 0.05$). The hazard ratio was the highest in positive nodes, followed by the stage of disease, intraoperative blood loss, and blood transfusion.

Discussion

In Japan, a subtotal esophagectomy with three-field lymph node dissection has been performed routinely as a curative

Table 3 Multivariate Cox regression analysis

Variable	Hazard ratio	95% CI	p
Sex	0.169	0.020–1.454	0.106
Age	1.088	0.976–1.214	0.129
Depth of tumor	0.240	0.037–1.559	0.135
Lymphatic invasion	0.243	0.026–3.485	0.393
Vascular invasion	0.239	0.021–2.745	0.250
Size of tumor	1.164	0.815–1.663	0.402
Positive lymph nodes	8.668	1.284–58.497	0.027*
Stage of the disease	5.439	1.665–17.763	0.005*
Blood transfusion	0.133	0.027–0.658	0.013*
Intraoperative blood loss	0.139	0.030–0.653	0.012*

* A value of $p < 0.05$ was considered to indicate a statistically significant difference with a 95% confidence interval (95% CI)

procedure in patients with esophageal SCC and reasonable functional status because the prognosis is highly associated with the presence of positive lymph nodes [7]. In contrast, true benefits of the extended lymph node dissection for patients with esophageal cancer remain controversial, especially in Western countries [2]. The concept of three-field lymphadenectomy has been established for the treatment of esophageal SCC in which lymph node metastases are found to locate almost equally at the abdomen through the neck. On the other hand, two-field lymphadenectomy is commonly performed in Western countries because of the high incidence of esophageal adenocarcinoma, which usually arises from the distal esophagus due to underlying gastroesophageal reflux disease followed by Barrett's esophagus; and the extension of lymph node involvement is often limited to the intrathoracic area. However, it is clear that the greater the number of lymph nodes obtained, the more accurately is the staging, and the prognosis can be determined [18]. In addition, it has been demonstrated that the number of metastatic lymph nodes and the ratio between metastatic and examined lymph nodes are independent prognostic factors [19].

Although proponents of a three-field lymphadenectomy believe it leads to better staging, decreased risk of local recurrence, and improvement of overall survival, most of previous reports regarding the outcomes of three-field lymphadenectomy were written based on single-institution experiences in a retrospective fashion, which was certainly subject to bias and obvious limitations [20, 21]. There is only one randomized controlled trial to compare two-field versus three-field lymphadenectomy in patients with esophageal SCC. It was conducted by Nishihira et al. [22], in which 62 patients were randomly assigned by a double-blind method to either the two-field group (n = 30) or the three-field group (n = 32). The authors concluded that three-field lymphadenectomy may reduce local recurrence and prolong survival after resection of thoracic esophageal

carcinoma, although it was not shown statistically. However, it is expected that the extension of lymph node dissection would be highly associated with the amount of intraoperative blood loss and the extended surgery is more likely to require blood transfusion.

Postoperative pulmonary complications are extremely common after esophagectomy, as in this study; and they potentially affect patients' quality of life and the prognosis. In this present study, most of the patients had a history of smoking and were expected to have poor pulmonary function preoperatively. To prevent postoperative pulmonary complications and improve the functional status, preoperative assessment of pulmonary functions is critical, and preoperative smoking cessation and aggressive pulmonary rehabilitation should be implemented. In addition, it is important to control the fluid balance between the intravascular and third space, avoiding failure of many organs such as lung, heart, and kidney due to volume overload. The perioperative management of fluid balance would be more difficult in patients with excessive intraoperative blood loss and/or blood transfusion. Two patients developed late pulmonary dysfunction due to interstitial pneumonia even at 3 months after surgery, suggesting that a prolonged time to recover from surgery is required, especially for patients with little pulmonary reserve.

There are several explanations for the negative effects of excessive blood loss on oncologic outcomes after surgery. Excessive intraoperative blood loss may cause tumor dissemination and potentially lead to local or systemic recurrence [23]. Some reports have suggested that intraoperative blood loss during curative gastrectomy for gastric cancer is a critical risk factor of recurrence [24]. Kamei et al. [25] reported that intraoperative blood loss, not blood transfusion, may have a specific association with peritoneal recurrence of gastric cancer—but not with other types of recurrence. In addition, Bruns et al. [26] demonstrated that >700 ml of blood loss significantly reduced natural killer cell function in patients who underwent gastrointestinal surgery. These studies suggested that intraoperative blood loss may impair the immune system locally and systemically, potentially leading to peritoneal recurrence of gastric cancer. In the present study, intrathoracic lymph node (bronchial lymph node) recurrence and lung metastasis were most commonly observed. Although peritoneal and/or pleural metastasis of esophageal cancer is not common, locally and/or systemically impaired immune system due to blood loss may be associated with lymph node recurrence and organ metastasis in the thoracic cavity.

Other studies have suggested that a large amount of blood loss may be associated with a longer period of systemic and local hypoperfusion, potentially leading to impaired oxygen delivery to vital organs such as lung, liver, and kidney. This may promote systemic inflammation,

which may prevent antitumor immunity [11]. Specifically, hemorrhagic shock has been reported to be associated with the elevated levels of interleukin-1 (IL-1), IL-6, and tumor necrosis factor-α, all of which could increase the risk for early postoperative mortality [11, 27, 28]. Younes et al. [29] reported that the number of intraoperative hypotensive episodes may negatively impact the long-term outcome after resection of colorectal cancer with liver metastasis. In the present study, no patients had a prolonged period of hypotension or hypovolemic shock during the surgery, and the intraoperative blood pressure was properly maintained with fluid resuscitation. However, patients who required blood transfusion may have a short period of local hypoperfusion in some organs such as liver and lung, potentially enhancing the recurrence or metastatic process via depression of the immune system.

Several reports have suggested that blood transfusion is a significant prognostic factor of outcomes in patients who underwent surgical resection of cancer [15, 16, 30, 31]. The mechanisms involved in the adverse effects of red blood cell transfusion may be related to impaired immunity or enhanced inflammation, which may lead to tumor growth or recurrence. The immunosuppressive effects with blood transfusion have been reported in patients with transplantation [32]. Kaplan et al. [33] demonstrated the increased activity and number of T-suppressor cells as well as the diminished natural killer cell activity in recipients of blood transfusions. The exact mechanisms of effects on the prognosis by both intraoperative blood loss and blood transfusion remain unknown. There may be unknown effects of intraoperative blood loss on the association between blood transfusion and decreased survival. Because patients with excessive intraoperative blood loss often require blood transfusion, intraoperative blood loss may be a more sensitive factor than blood transfusion. However, there is a possibility of measurement and selection bias regarding these two variables. Further studies with a larger sample size are required to determine the true impact of intraoperative blood loss and transfusion on the long-term outcome after radical esophagectomy in patients with SCC

Finally, although the incidence of lymph node recurrence and/or remote organ metastasis was comparable between the BG (8/19) and LBG (8/18) groups, the prognosis for the BG group was significantly worse than that for the LBG group. This may be explained by the fact that more patients in the BG group had remote metastasis compared to those in the LBG group. Osugi et al. [34] reported that patients with local lymphatic recurrence survived longer than patients with remote metastasis, suggesting that remote metastasis contributes more to survival compared to local lymph node recurrence. This further supports our results.

Conclusions

The present study demonstrates that the survival rate is significantly worse among patients with a large intraoperative blood loss (≥510 g) requiring blood transfusion compared to that in patients with less blood loss (<510 g) even though the distribution of the stage of disease, the number of positive lymph nodes and presence of lymphovascular invasions is comparable between the groups. Systemic inflammation and impaired immunity induced by local and/or systemic hypoperfusion due to blood loss and the following blood transfusion may promote growth of any residual tumor after surgery. Although surgical resection should be the primary choice for patients with a resectable esophageal SCC and reasonable functional status, every effort should be made to reduce intraoperative blood loss requiring blood transfusion as it may be associated with decreased long-term survival.

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