ANTICANCER RESEARCH *43*: 5173-5179 (2023)
doi:10.21873/anticanres.16718

Intraoperative Blood Loss Impacts Recurrence and Survival in Patients With Locally Advanced Esophageal Cancer

HAYATO WATANABE[1,2], KAZUKI KANO[1,2], ITARU HASHIMOTO[1,2], MIE TANABE[1,2], SHIZUNE ONUMA[1,2], JUNYA MORITA[1,2], SHINSUKE NAGASAWA[1,2], KYOHEI KANEMATSU[1], TORU AOYAMA[1,2], TAKANOBU YAMADA[1,2], TAKASHI OGATA[1], YASUSHI RINO[2], AYA SAITO[2] and TAKASHI OSHIMA[1]

[1]*Department of Gastrointestinal Surgery, Kanagawa Cancer Center, Yokohama, Japan;*
[2]*Department of Surgery, Yokohama City University, Yokohama, Japan*

Abstract. *Background/Aim: Intraoperative blood loss (IBL) has been reported to decrease survival after surgical resection of some malignancies; however, there are few reports on the effects of IBL on recurrence and survival in locally advanced esophageal cancer. Therefore, we investigated the relationship between IBL and postoperative recurrence and overall survival in patients who underwent surgery for esophageal cancer. Patients and Methods: One hundred and ninety-eight patients with locally advanced esophageal cancer who underwent preoperative adjuvant chemotherapy and curative resection as standard treatment were included in this study. Based on a defined cut-off value for IBL, 27 and 171 patients were classified into the high and low IBL groups, respectively. The relationship between each group and clinicopathological factors, postoperative recurrence, and overall survival were investigated. Results: In terms of the relationship between IBL and clinicopathological factors, the high IBL group had significantly more patients with pathological T4, longer operative time, and higher incidence of postoperative complications than the low IBL group. Both recurrence-free and overall survival were significantly worse in the high IBL group than in the low IBL group. Furthermore, multivariate analysis identified high IBL as an independent factor for predicting poor reference free survival and overall survival. Conclusion: Heavy IBL in patients with locally advanced esophageal cancer may be a useful predictor of postoperative recurrence and overall survival.*

Correspondence to: Takashi Oshima, Department of Gastrointestinal Surgery, Kanagawa Cancer Center, 2-3-2, Nakao, Asahi-ku, Yokohama, Kanagawa 241-8515, Japan. Tel: +81 455202222, Fax: +81 455202202, e-mail: oshimat@kcch.jp

Key Words: Esophageal squamous cell carcinoma, intraoperative blood loss, survival.

Esophageal cancer is the seventh most common cancer worldwide and the sixth leading cause of cancer-related death (1). It is estimated that more than 600,000 new cases and 400,000 deaths occur annually worldwide (2). The standard treatment for locally advanced esophageal cancer is a multimodal treatment consisting of neoadjuvant chemotherapy (NAC) and curative esophagectomy with lymph node dissection (3-6). The goal of NAC is to control micrometastases that may not be surgically resected prior to surgery (7, 8). However, despite multimodal treatment, the prognosis of patients with esophageal cancer remains unsatisfactory. Thus, to further improve survival, the search for predictive biomarkers for patients with locally advanced esophageal squamous cell carcinoma (ESCC), and personalized treatments based thereon, may be helpful in improving their outcomes.

In addition to stage, poor postoperative survival factors in patients with cancer have been reported to include poor nutritional status (9, 10), presence of postoperative complications (11, 12), and intraoperative bleeding loss (IBL). These factors have also been reported to decrease survival after surgical resection of some malignancies, including esophageal squamous cell carcinoma (ESCC) (13-16). However, there are few reports on the impact of IBL and transfusion on the recurrence and survival of patients with locally advanced ESCC.

Therefore, in the present study, we examined the association between IBL and recurrence and survival in patients with ESCC treated with standard therapy.

Patients and Methods

Ethical approval. This study was approved by the Institutional Review Board (IRB) of Kanagawa Cancer Center prior to initiation (Approval No.: 2021 Epidemiological Study 104). This study was conducted in accordance with the principles of the Declaration of Helsinki. All participants provided written informed consent.

Eligible patients. A total of 540 consecutive patients with esophageal cancer who underwent esophagectomy at Kanagawa

Cancer Center between January 2011 and December 2019 were selected for this study using the following inclusion criteria: 1) tumor located in the thoracic esophagus and histopathologically diagnosed as primary esophageal squamous cell carcinoma, and 2) primary esophageal cancer diagnosed according to the International Union Against Cancer TNM classification 8th edition (3, 17), undergoing radical resection (R0) after NAC with cisplatin + 5-fluorouracil followed by radical lymph node resection. The exclusion criteria were as follows: 1) NAC other than cisplatin + 5-fluorouracil, 2) non-curative R1 or R2 resection, and 3) cases in which esophagectomy was performed as salvage treatment.

Preoperative adjuvant chemotherapy, surgery, and postoperative follow-up. Based on the Japan Clinical Oncology Group (JCOG) 9907 study and clinical trials (6), NAC was administered preoperatively to patients with stage II or III esophageal cancer. Cisplatin plus 5-fluorouracil was administered twice every 3 weeks as NAC. Surgical resection was usually performed 4-6 weeks after the completion of NAC. As a rule, open subtotal esophagectomy *via* right thoracotomy, reconstruction of the gastrointestinal tube *via* the retrosternal or posterior mediastinal route, and cervical anastomosis were performed. Lymph node dissection was generally performed in the abdomen, thorax, and neck. In the case of lower esophageal cancer, lymph node dissection was performed in the abdomen and thorax; the neck was excluded. An enteral feeding tube was placed in the stomach or duodenum for enteral nutrition. Postoperative follow-up was performed every 3 months for the first year, and every 6 months for the second to fifth years. Physical examination, blood tests (including tumor markers), and computed tomography (CT) of the neck and abdomen were performed every 6 months for 2 years postoperatively and then at least every year thereafter until 5 years postoperatively to evaluate for recurrence. Endoscopy was performed every year until 5 years postoperatively. Positron emission tomography-CT was performed if recurrence was suspected.

Clinicopathological data. All data were retrieved from a clinicopathological database based on patient records. Body mass index (BMI) and American Society of Anesthesiologists physical status (ASA-PS) data were routinely collected before surgery. Postoperative infectious complications (PIC) occurring during hospitalization or within 30 days after surgery were evaluated according to the Clavien–Dindo classification (18). Anastomotic leakage, pneumonia, abdominal abscess, surgical site infection, and/or severe pyothorax of degree II or higher were defined as PIC.

The pathological response to NAC was evaluated according to the pathological criteria of the Japanese Esophageal Society (JES) for the effects of chemotherapy (19) and classified into the following six categories: Grade 3: no viable cancer cells were observed; Grade 2: viable cancer cells comprised <1/3 of the tumor tissue and other cancer cells were highly degenerated or necrotic; Grade 1b: viable cancer cells comprised between 1/3 and 2/3 of the tumor tissue; Grade 1a: viable cancer cells comprised >2/3 of the tumor tissue; Grade 0: no cytologic or histologic response to therapy. Patients with a grade 2 or 3 pathological response to NAC were classified as responders, and patients with grades 0, 1a, or 1b were classified as non-responders.

Grouping by IBL. IBL was calculated by adding the amount of blood aspirated from the surgical field using a suction pump and the amount of blood absorbed by gauze during surgery; optimal cut-off values for IBL and recurrence-free survival (RFS) were defined using X-tile software (Yale School of Medicine, New Haven, CT, USA) (20). The optimal cut-off value for IBL for recurrence was defined as 850 ml, and patients were divided into two groups according to this cut-off value: low IBL group, IBL <850 ml; high IBL group, IBL ≥850 ml.

Statistical analyses. Fisher's exact and chi-square tests were used to compare the clinicopathological characteristics of the patients in the low and high IBL groups. The optimal cut-off point for IBL was selected using the minimum *p*-value method, and the internal validity of the cut-off point was evaluated using a two-fold cross-validation approach (20). Overall survival (OS) was defined as the time from the initiation of NAC treatment to the date of death from any cause or the last follow-up date, while RFS was defined as the time from the initiation of NAC treatment to the date of recurrence or death (whichever occurred first) or the last follow-up date. Data for patients with no events by the last follow-up date were censored. Kaplan–Meier graphs were used to calculate OS and RFS rates, and log-rank tests were used to compare the differences in survival rates. Cox proportional hazards regression models were used for univariate and multivariate analyses of RFS and OS. All statistical tests were two-tailed and EZR ver. 1.37 (Jichi Medical University, Tochigi, Japan) was used for all statistical analyses (21). *p*-Values <0.05 were considered statistically significant.

Results

Patients. A total of 220 patients diagnosed with clinical stage II or III esophageal squamous cell carcinoma who underwent esophagectomy after NAC were identified as candidates for this study. Of these, 22 patients were excluded: 13 patients who received triple chemotherapy in a clinical trial, eight patients who underwent non-curative resection, and one patient whose postoperative pathological diagnosis included neuroendocrine carcinoma. Finally, 198 patients were included in this study (Figure 1). Twenty-seven and 171 patients were classified into the high and low IBL groups, respectively, according to the IBL cut-off values. The median follow-up was 41.40 months [interquartile range (IQR)=5.10-127.90].

Differences in clinicopathological features according to IBL. Table I compares the clinicopathological characteristics between the low and high IBL groups. The high IBL group had significantly more T4 factors (p<0.001), a significantly longer operative time (p<0.001), and a significantly higher incidence of PIC (p=0.004).

Relationship between IBL and RFS and OS. The RFS of the high IBL group was significantly poorer than that of the low IBL group (p=0.002; Figure 2). The OS of the high IBL group was significantly poorer than that of the low IBL group (p=0.010; Figure 3).

Univariate and multivariate analysis of RFS and OS. In the univariate analysis of RFS, operative time, IBL, pathological T factor, pathological N factor, and histologic response were

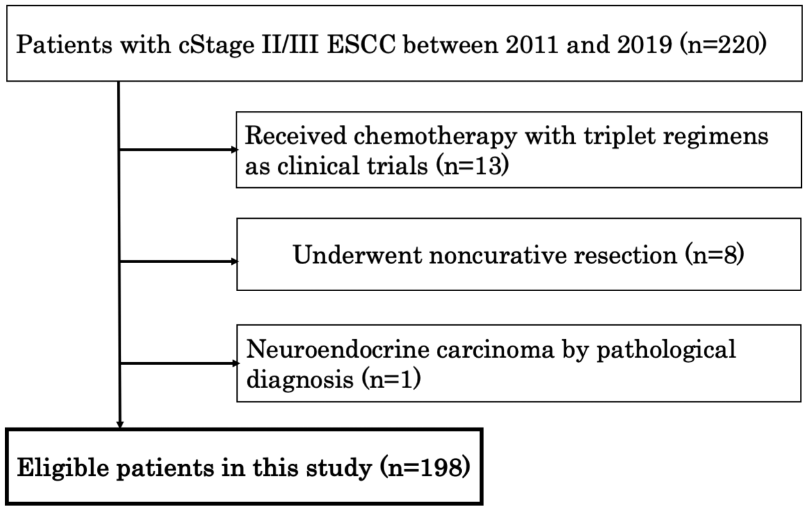

Figure 1. *Flow chart of patient selection. In total, 220 patients diagnosed with clinical stage II or III esophageal squamous cell carcinoma and underwent curative esophagectomy after neoadjuvant chemotherapy were eligible for inclusion. Of these, 22 patients were excluded: 13 patients who received triple chemotherapy in a clinical trial, eight patients who underwent non-curative resection, and one patient whose postoperative pathological diagnosis included neuroendocrine carcinoma. Finally, a total of 198 patients were included in this study. ESCC: Esophageal squamous cell carcinoma.*

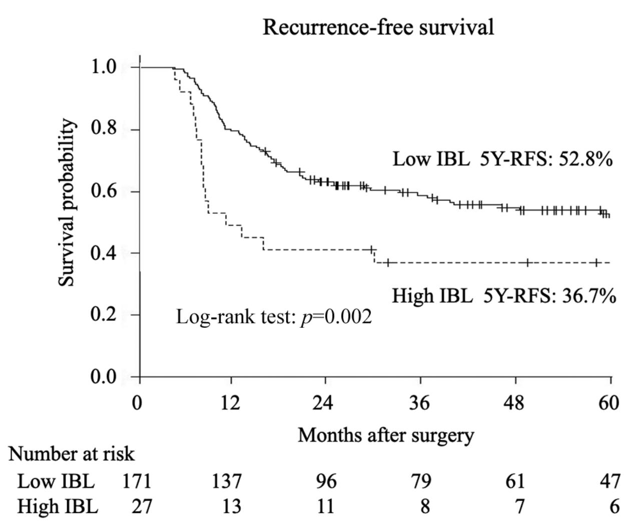

Figure 2. *Recurrence-free survival (RFS) in the high and low IBL groups. The RFS in the high intraoperative blood loss (IBL) group was significantly poorer than that in the low IBL group (p=0.002, log-rank test).*

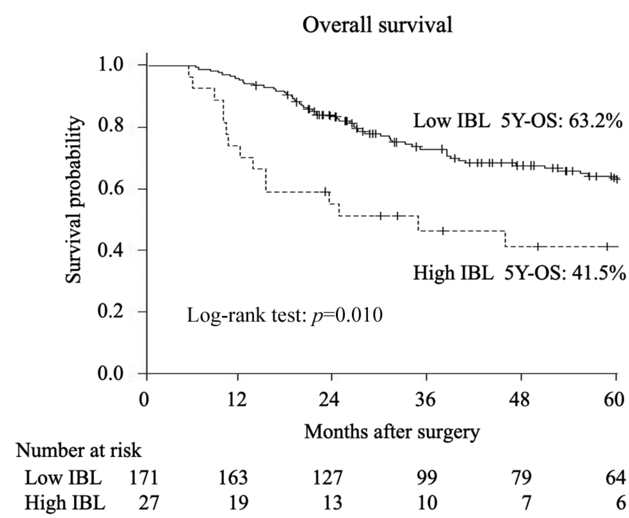

Figure 3. *Overall survival (OS) in the high and low intraoperative blood loss (IBL) groups. The OS in the high IBL group was significantly poorer than that in the low IBL group (p=0.010, log-rank test).*

selected as risk factors for recurrence; in the multivariate analysis, IBL, pathological T factor, and pathological N factor were independent risk factors for RFS (Table II). In the univariate analysis of OS, sex, IBL, pathological T factor, pathological N factor, and PIC were shown to be risk factors for poor OS; in the multivariate analysis, IBL, pathological T factor, pathological N factor, and PIC were independent poor prognostic factors for OS (Table III).

Discussion

In this study, we determined the association between IBL and recurrence and survival in patients with ESCC treated with standard therapy. Results showed that the high IBL group had significantly worse RFS and OS rates than the low IBL group. Furthermore, in the multivariate analysis, high IBL was an independent risk factor for recurrence and poor survival.

Table I. *Association between intraoperative blood loss and clinicopathological features*.

	All patients (n=198)	IBL		*p*-Value
		High (>850 ml) (n=27)	Low (<850 ml) (n=171)	
Age (years), median (IQR)	67 (45-79)	69 (56-78)	67 (45-79)	0.993
Sex				0.119
Female	37 (19.0%)	2 (7.7%)	35 (20.7%)	
Male	161 (81.0%)	25 (92.3%)	136 (79.3%)	
BMI, median (IQR)	21.4 (13.7-28.9)	21.6 (13.7-28.9)	21.2 (14.4-28.7)	1.000
ASA-PS				0.653
1	26 (13.3%)	3 (11.5%)	23 (13.6%)	
2	168 (84.6%)	23 (84.6%)	144 (85.2%)	
3	4 (2.1%)	1 (3.8%)	3 (1.8%)	
Main tumor location				0.654
Ut	27 (13.3%)	4 (11.5%)	23 (13.6%)	
Mt	104 (52.3%)	16 (61.5%)	88 (50.9%)	
Lt	67 (34.4%)	7 (26.9%)	60 (35.5%)	
Tumor size (mm), median (IQR)	38 (0-115)	40 (0-115)	36 (0-105)	0.214
Pathological T factor				<0.001
T0	9 (4.6%)	0 (0.0%)	9 (5.3%)	
T1	50 (24.6%)	7 (23.1%)	43 (24.9%)	
T2	30 (15.4%)	3 (11.5%)	27 (16.0%)	
T3	94 (47.7%)	10 (38.5%)	84 (49.1%)	
T4	15 (7.7%)	7 (26.9%)	8 (4.7%)	
Pathological N factor				0.329
N0	68 (34.4%)	7 (26.9%)	61 (35.5%)	
N1	71 (35.9%)	10 (38.5%)	61 (35.5%)	
N2	30 (15.4%)	3 (11.5%)	27 (16.0%)	
N3	29 (14.4%)	7 (23.1%)	22 (13.0%)	
Pathological stage				0.076
0	5 (2.6%)	0 (0.0%)	5 (3.0%)	
I	21 (11.8%)	3 (11.5%)	18 (10.1%)	
II	63 (32.3%)	6 (23.1%)	57 (33.7%)	
III	73 (36.9%)	9 (33.3%)	64 (37.3%)	
IV	36 (20.7%)	9 (33.3%)	27 (16.0%)	
Pathological response				0.164
0	8 (4.1%)	2 (7.7%)	6 (3.6%)	
1a	108 (54.9%)	18 (69.2%)	89 (52.7%)	
1b	27 (13.3%)	2 (7.7%)	25 (14.2%)	
2	46 (23.1%)	4 (15.4%)	42 (24.3%)	
3	9 (4.6%)	0 (0.0%)	9 (5.3%)	
Operation time (min), median (IQR)	430 (283-647)	481 (388-647)	412 (283-619)	<0.001
Postoperative infectious complications				0.004
Grade II or none	144 (73.3%)	13 (46.2%)	131 (77.5%)	
Grade III or more	54 (26.7%)	14 (53.8%)	40 (22.5%)	

IBL: Intraoperative blood loss; BMI: body mass index; IQR: interquartile range; ASA-PS: American Society of Anesthesiologists Physical Status.

Excessive IBL predicts poor survival after surgical resection of several malignancies, including ESCC (13-16). Although the mechanisms by which massive IBL during cancer surgery affects postoperative recurrence and prognosis are not entirely clear, several hypotheses have been postulated. The first is the suppression of the patient's immune system caused by intraoperative hemorrhage and subsequent blood transfusion. It has been reported that massive blood loss decreases the activity of natural killer cells through the loss of plasma components, and that blood transfusion decreases the function of T cells, which is associated with tumor progression (21, 22). Suppression of the immune system may make it difficult to eliminate residual cancer cells, thus increasing the risk of recurrence and potentially leading to poorer OS. Second, it may promote hematogenous metastasis and dissemination. Heavy IBL increases the risk of cancer cell spread from the abdominal cavity to other sites *via* the bloodstream during

Table II. *Univariate and multivariate analyses of the prognostic influence of clinicopathological features on recurrence-free survival.*

		Univariate analysis			Multivariate analysis		
	No. of patients	HR	95%CI	*p*-Value	HR	95%CI	*p*-Value
Age (years)				0.527			0.473
<67	93	1			1		
≥67	105	1.141	0.758-1.719		0.857	0.563-1.306	
Sex				0.149			0.666
Female	37	1			1		
Male	161	1.520	0.861-2.685		0.873	0.471-1.617	
BMI				0.182			0.313
≥22	82	1			1		
<22	116	1.331	0.875-2.025		1.250	0.810-1.935	
ASA-PS				0.243			0.758
1	26	1			1		
2/3	172	1.506	0.757-2.996		1.119	0.550-2.280	
Main tumor location				0.595			0.991
Lt/Mt	171	1			1		
Ut	27	1.162	0.668-2.020		0.997	0.550-1.807	
Operation time (min)				0.027			0.094
<400 min	76	1			1		
≥400 min	122	1.651	1.059-2.573		1.525	0.931-2.499	
IBL (ml)				0.003			0.039
<850	171	1			1		
≥850	27	2.197	1.312-3.679		1.811	1.030-3.184	
Pathological T factor				0.001			0.035
T0/1/2	89	1			1		
T3/4	109	2.130	1.383-3.282		1.659	1.038-2.654	
Pathological N factor				<0.001			<0.001
N0	68	1			1		
N1/2/3	130	4.293	2.428-7.590		3.848	2.107-7.026	
Pathological response				0.001			0.290
0/1a/1b	143	1			1		
2/3	55	0.415	0.242-0.711		0.723	0.397-1.318	
PIC				0.092			0.637
Grade II or none		1			1		
Grade III or more		1.466	0.9401-2.286		1.123	0.694-1.819	

HR: Hazard ratio; CI: confidence interval; BMI: body mass index; ASA-PS: American Society of Anesthesiologists Physical Status; IBL: intraoperative blood loss; PIC: postoperative infectious complications.

surgical manipulation. The possibility of cancer cells entering the bloodstream or lymphatic flow or causing peritoneal seeding is more likely when the tumor tissue is being manipulated. Furthermore, a massive hemorrhage may obscure the visual field, making complete resection of the tumor difficult. Incomplete resection increases the risk of recurrence due to the growth of residual tumor cells. Third, an association between surgical stress and tumor growth have also been reported. The physical stress associated with surgery and massive blood loss may promote cancer growth and metastasis. For example, hormones and cytokines secreted in response to stress promote cancer growth and metastasis (23-25). Fourth, delayed postoperative recovery owing to massive blood loss may compromise the nutritional status of patients. Malnutrition may delay the initiation of postoperative adjuvant chemotherapy and cause sarcopenia, potentially leading to other morbidities and death (26).

This study has several limitations. First, it was a single-center, retrospective study with a relatively small sample size. Second, because this study was conducted over a relatively long period (2011-2019), there may be a historical bias in the treatment strategies and perioperative management, which could have influenced the short-term outcomes after esophagectomy. Third, although we used the minimum *p*-value method to determine the cut-off value for IBL, various cut-off values have been employed in previous studies, and the optimal reproducible cut-off value remains unclear.

Table III. *Univariate and multivariate analyses of prognostic influence of the clinicopathological features on overall survival*.

		Univariate analysis			Multivariate analysis		
	No. of patients	HR	95%CI	*p*-Value	HR	95%CI	*p*-Value
Age (years)				0.235			0.343
<67	93	1			1		
≥67	105	1.308	0.839-2.308		1.246	0.791-1.964	
Sex				0.044			0.153
Female	37	1			1		
Male	161	2.043	1.021-4.088		1.737	0.815-3.702	
BMI				0.069			0.060
≥22	82	1			1		
<22	116	1.533	0.967-2.428		1.578	0.980-2.539	
ASA-PS				0.250			0.332
1	26	1			1		
2/3	172	1.535	0.739-3.189		1.456	0.682-3.111	
Main tumor location				0.629			0.269
Lt/Mt	171	1			1		
Ut	27	0.849	0.438-1.649		0.674	0.335-1.356	
Operation time (min)				0.609			0.519
<400 min	76	1			1		
≥400 min	122	1.125	0.716-1.768		0.846	0.508-1.407	
IBL (ml)				0.011			0.021
<850	171	1			1		
≥850	27	2.068	1.178-3.629		2.091	1.120-3.906	
Pathological T factor				0.002			0.046
T0/1/2	89	1			1		
T3/4	109	2.071	1.302-3.295		1.711	1.009-2.903	
Pathological N factor				<0.001			0.001
N0	68	1			1		
N1/2/3	130	3.403	1.878-6.167		2.896	1.529-5.483	
Pathological response				0.057			0.670
0/1a/1b	143	1			1		
2/3	55	0.600	0.355-1.015		1.140	0.625-2.079	
PIC				0.009			0.060
Grade II or none		1			1		
Grade III or more		1.876	1.170-3.007		1.638	0.978-2.745	

HR: Hazard ratio; CI: confidence interval; BMI: body mass index; ASA-PS: American Society of Anesthesiologists Physical Status; IBL: intraoperative blood loss; PIC: postoperative infectious complications.

Conclusion

IBL may be a useful independent risk factor for recurrence in patients with locally advanced ESCC who have undergone radical resection after NAC. A prospective multicenter study with a large sample size is required in the future to validate whether massive bleeding is a predictor of recurrence and prognosis.

Conflicts of Interest

The Authors declare no conflicts of interest or financial ties in relation to this study.

Authors' Contributions

Conceptualization: HW and KK; data collection and literature searches: HW, KK, MT, SO, JM, SN, KK, and TY. Data analysis and interpretation: HW, KK, IH, TA, and TO. All researchers interpreted the data. HW and TO drafted the paper and figures, respectively. Finally, the paper was revised and approved by all the researchers. All Authors actively participated in this study.

Acknowledgements

The Authors thank the patients, their families, and the staff at Kanagawa Cancer Center for their participation in this study.

References

1 Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F: Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71(3): 209-249, 2021. DOI: 10.3322/caac.21660

2 Smyth EC, Lagergren J, Fitzgerald RC, Lordick F, Shah MA, Lagergren P, Cunningham D: Oesophageal cancer. Nat Rev Dis Primers 3: 17048, 2017. DOI: 10.1038/nrdp.2017.48

3 Bosset JF, Gignoux M, Triboulet JP, Tiret E, Mantion G, Elias D, Lozach P, Ollier JC, Pavy JJ, Mercier M, Sahmoud T: Chemoradiotherapy followed by surgery compared with surgery alone in squamous-cell cancer of the esophagus. N Engl J Med 337(3): 161-167, 1997. DOI: 10.1056/NEJM199707173370304

4 Burmeister BH, Smithers BM, Gebski V, Fitzgerald L, Simes RJ, Devitt P, Ackland S, Gotley DC, Joseph D, Millar J, North J, Walpole ET, Denham JW, Trans-Tasman Radiation Oncology Group, Australasian Gastro-Intestinal Trials Group: Surgery alone versus chemoradiotherapy followed by surgery for resectable cancer of the oesophagus: a randomised controlled phase III trial. Lancet Oncol 6(9): 659-668, 2005. DOI: 10.1016/S1470-2045(05)70288-6

5 Medical Research Council Oesophageal Cancer Working Group: Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomised controlled trial. Lancet 359(9319): 1727-1733, 2002. DOI: 10.1016/S0140-6736(02)08651-8

6 Ando N, Kato H, Igaki H, Shinoda M, Ozawa S, Shimizu H, Nakamura T, Yabusaki H, Aoyama N, Kurita A, Ikeda K, Kanda T, Tsujinaka T, Nakamura K, Fukuda H: A randomized trial comparing postoperative adjuvant chemotherapy with cisplatin and 5-fluorouracil versus preoperative chemotherapy for localized advanced squamous cell carcinoma of the thoracic esophagus (JCOG9907). Ann Surg Oncol 19(1): 68-74, 2012. DOI: 10.1245/s10434-011-2049-9

7 Yano M, Takachi K, Doki Y, Miyashiro I, Kishi K, Noura S, Eguchi H, Yamada T, Ohue M, Ohigashi H, Sasaki Y, Ishikawa O, Imaoka S: Preoperative chemotherapy for clinically node-positive patients with squamous cell carcinoma of the esophagus. Dis Esophagus 19(3): 158-163, 2006. DOI: 10.1111/j.1442-2050.2006.00558.x

8 Yoshikawa T, Sasako M, Yamamoto S, Sano T, Imamura H, Fujitani K, Oshita H, Ito S, Kawashima Y, Fukushima N: Phase II study of neoadjuvant chemotherapy and extended surgery for locally advanced gastric cancer. Br J Surg 96(9): 1015-1022, 2009. DOI: 10.1002/bjs.6665

9 Aoyama T, Hara K, Kazama K, Maezawa Y: Clinical impact of nutrition and inflammation assessment tools in gastric cancer treatment. Anticancer Res 42(11): 5167-5180, 2022. DOI: 10.21873/anticanres.16023

10 Kuwada K, Kuroda S, Kikuchi S, Yoshida R, Nishizaki M, Kagawa S, Fujiwara T: Clinical impact of sarcopenia on gastric cancer. Anticancer Res 39(5): 2241-2249, 2019. DOI: 10.21873/anticanres.13340

11 Maezawa Y, Aoyama T, Ju M, Komori K, Kano K, Sawazaki S, Numata M, Hayashi T, Yamada T, Tamagawa H, Sato T, Ogata T, Cho H, Oshima T, Yukawa N, Yoshikawa T, Masuda M, Rino Y: The impact of severe infectious complications on long-term prognosis for gastric cancer. Anticancer Res 40(7): 4067-4074, 2020. DOI: 10.21873/anticanres.14404

12 Aoyama T, Murakawa M, Katayama Y, Yamaoku K, Kanazawa A, Higuchi A, Shiozawa M, Morimoto M, Yoshikawa T, Yamamoto N, Rino Y, Masuda M, Morinaga S: Impact of postoperative complications on survival and recurrence in pancreatic cancer. Anticancer Res 35(4): 2401-2409, 2015.

13 Liang YX, Guo HH, Deng JY, Wang BG, Ding XW, Wang XN, Zhang L, Liang H: Impact of intraoperative blood loss on survival after curative resection for gastric cancer. World J Gastroenterol 19(33): 5542-5550, 2013. DOI: 10.3748/wjg.v19.i33.5542

14 Whooley BP, Law S, Murthy SC, Alexandrou A, Wong J: Analysis of reduced death and complication rates after esophageal resection. Ann Surg 233(3): 338-344, 2001. DOI: 10.1097/00000658-200103000-00006

15 Hyung WJ, Noh SH, Shin DW, Huh JHJ, Huh BJ, Choi SH, Min JS: Adverse effects of perioperative transfusion on patients with stage III and IV gastric cancer. Ann Surg Oncol 9(1): 5-12, 2002. DOI: 10.1245/aso.2002.9.1.5

16 Law S, Wong KH, Kwok KF, Chu KM, Wong J: Predictive factors for postoperative pulmonary complications and mortality after esophagectomy for cancer. Ann Surg 240(5): 791-800, 2004. DOI: 10.1097/01.sla.0000143123.24556.1c

17 Rice TW, Patil DT, Blackstone EH: 8th edition AJCC/UICC staging of cancers of the esophagus and esophagogastric junction: application to clinical practice. Ann Cardiothorac Surg 6(2): 119-130, 2017. DOI: 10.21037/acs.2017.03.14

18 Dindo D, Demartines N, Clavien PA: Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 240(2): 205-213, 2004. DOI: 10.1097/01.sla.0000133083.54934.ae

19 Society JE: Japanese Classification of Esophageal Cancer, 11th edn: part I. Tokyo, Kanehara & Co., Ltd, 2017.

20 Mazumdar M, Smith A, Bacik J: Methods for categorizing a prognostic variable in a multivariable setting. Stat Med 22(4): 559-571, 2003. DOI: 10.1002/sim.1333

21 Kanda M, Kobayashi D, Tanaka C, Iwata N, Yamada S, Fujii T, Nakayama G, Sugimoto H, Koike M, Nomoto S, Murotani K, Fujiwara M, Kodera Y: Adverse prognostic impact of perioperative allogeneic transfusion on patients with stage II/III gastric cancer. Gastric Cancer 19(1): 255-263, 2016. DOI: 10.1007/s10120-014-0456-x

22 Nakanishi K, Kanda M, Kodera Y: Long-lasting discussion: Adverse effects of intraoperative blood loss and allogeneic transfusion on prognosis of patients with gastric cancer. World J Gastroenterol 25(22): 2743-2751, 2019. DOI: 10.3748/wjg.v25.i22.2743

23 Lee JW, Shahzad MM, Lin YG, Armaiz-Pena G, Mangala LS, Han HD, Kim HS, Nam EJ, Jennings NB, Halder J, Nick AM, Stone RL, Lu C, Lutgendorf SK, Cole SW, Lokshin AE, Sood AK: Surgical stress promotes tumor growth in ovarian carcinoma. Clin Cancer Res 15(8): 2695-2702, 2009. DOI: 10.1158/1078-0432.CCR-08-2966

24 Kumagai Y, Ohzawa H, Miyato H, Horie H, Hosoya Y, Lefor AK, Sata N, Kitayama J: Surgical stress increases circulating low-density neutrophils which may promote tumor recurrence. J Surg Res 246: 52-61, 2020. DOI: 10.1016/j.jss.2019.08.022

25 Tsuchiya Y, Sawada S, Yoshioka I, Ohashi Y, Matsuo M, Harimaya Y, Tsukada K, Saiki I: Increased surgical stress promotes tumor metastasis. Surgery 133(5): 547-555, 2003. DOI: 10.1067/msy.2003.141

26 Laviano A, Gori C, Rianda S: Sarcopenia and nutrition. Adv Food Nutr Res 71: 101-136, 2014. DOI: 10.1016/B978-0-12-800270-4.00003-1

Received September 3, 2023
Revised September 19, 2023
Accepted September 20, 2023