Factors Affecting Blood Loss During Thoracoscopic Esophagectomy for Esophageal Carcinoma

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Background: Major intraoperative hemorrhage reportedly predicts unfavorable survival outcomes following surgical resection for esophageal carcinoma (EC). However, the factors predicting the amount of blood lost during thoracoscopic esophagectomy have yet to be sufficiently studied. We sought to identify risk factors for excessive blood loss during video-assisted thoracoscopic surgery (VATS) for EC.
Methods: Using simple and multiple linear regression models, we performed retrospective analyses of the associations between clinicopathological/surgical factors and estimated hemorrhagic volume in 168 consecutive patients who underwent VATS-type esophagectomy for EC.
Results: The median blood loss amount was 225 mL (interquartile range, 126–380 mL). Abdominal laparotomy (p<0.001), thoracic duct resection (p=0.014), and division of the azygos arch (p<0.001) were significantly related to high volumes of blood loss. Body mass index and operative duration, as continuous variables, were also correlated positively with blood loss volume in simple linear regression. The multiple linear regression analysis identified prolonged operative duration (p<0.001), open laparotomy approach (p=0.003), azygos arch division (p=0.005), and high body mass index (p=0.014) as independent predictors of higher hemorrhage amounts during VATS esophagectomy.
Conclusion: As well as body mass index, operation-related factors such as operative duration, open laparotomy, and division of the azygos arch were independently predictive of estimated blood loss during VATS esophagectomy for EC. Laparoscopic abdominal procedures and azygos arch preservation might be minimally invasive options that would potentially reduce intraoperative hemorrhage, although oncological radicality remains an important consideration.

Keywords: Azygos arch, Blood volume, Esophageal neoplasms, Esophageal surgery, Thoracoscopy

Introduction

Thoracic esophagectomy, despite being a mainstay in the management of esophageal carcinoma (EC), is one of the most challenging surgical procedures and is associated with high morbidity and mortality rates [1,2]. Several patient factors, such as advanced age, sarcopenia, impaired respiratory function, and renal failure, have been reported to be predictive of rescue failure after thoracic esophagectomy [2-4]. As an operation-related factor, high intraoperative blood loss volume has been recognized as conferring a risk of complications and death in patients undergoing esophagectomy for EC [5,6]. Taking measures to regulate bleeding during this surgery is hence of prognostic significance.

Minimally invasive esophagectomy (MIE), such as the video-assisted thoracoscopic surgery (VATS) technique, has been developed to reduce surgical stress and optimize postoperative recovery [7-9] and is associated with less blood loss than occurs in open esophagectomy [10-12]. The interests of surgeons thus include strategies for lowering intraoperative hemorrhagic volume during MIE. However,

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the factors correlated with the amount of blood loss during thoracoscopic esophagectomy have yet to be fully investigated.

In the present study, we retrospectively assessed the relationships between clinicopathological/surgical features and the amount of intraoperative blood loss in patients undergoing VATS esophagectomy for EC in an attempt to identify risk factors for excessive bleeding.

Methods

Study population

Employing a database prospectively constructed by the Department of Gastroenterological Surgery, Toranomon Hospital, we identified 211 consecutive patients who had undergone VATS esophagectomy for esophageal malignancies (R0/R1) between October 2015 and December 2019. Of these, 9 cases involving surgical resection of carcinosarcoma (n=3), malignant melanoma (n=2), neuroendocrine carcinoma (n=2), salivary gland–type carcinoma (n=1), and hepatoid carcinoma (n=1) were regarded as ineligible for this study. Patients who underwent only lower esophageal resection (n=8), robot-assisted MIE (n=4), or multiorgan resection (n=4) were excluded from the analysis. Subjects with liver cirrhosis (n=5), renal failure requiring regular hemodialysis (n=1), hematological disorders (n=1), and preoperative antiplatelet/anticoagulant therapy (n=11) were also excluded. The remaining 168 patients were retrospectively reviewed and included in this study.

All of the analyses were conducted in accordance with the ethical guidelines for clinical studies in Japan and the Declaration of Helsinki under approval of the Institutional Review Board of Toranomon Hospital (approval no., 2102). Written informed consent was not necessary because of the retrospective design of the present study.

Operative procedure

Our first choice when performing thoracic esophageal resection for EC was VATS esophagectomy, if it was judged to be feasible [13]. In this operation, we carried out 2- or 3-field lymph node dissection, balancing the extent of tumor progression and potential surgical risk. The thoracoscopic procedure was generally conducted with the patient in the left lateral position [8,9], with artificial pneumothorax. As the abdominal approach, either open laparotomy or a laparoscopic technique, including hand-assisted laparoscopic surgery, was selected as appropriate for individual cases. The most common esophageal replacement was a gastric conduit, but colon interposition was also an option [14,15]. The esophageal substitute was pulled up via a retrosternal route or a posterior mediastinal route, and a cervical hand-sewn anastomosis was subsequently created.

We preserved the thoracic duct in cases of clinical stage I EC, according to the TNM (tumor-node-metastasis) classification (Union for International Cancer Control, seventh edition) [16], and otherwise endeavored to resect the duct for the purpose of lymphadenectomy if this was considered to be tolerable for the patient [17]. The azygos arch, an important anatomical landmark crossing over the esophagus when approached from the right thoracic cavity, was formerly ligated and severed to facilitate surgical exposure and maximum esophageal mobilization [18], and this technique is still employed at many other institutions [8-11,19]. In 2018, however, we tentatively introduced a new surgical policy attempting to leave the azygos arch intact, for as long as possible, while performing the VATS technique. The background objective of azygos arch preservation (AAP) was to prevent unintended injury of the right bronchial artery, which reportedly has a strong association with transection of the azygos arch [20,21]. Regardless of whether the azygos arch was preserved, we intended to keep the right bronchial artery intact in order to maintain the blood supply to the bronchus (Fig. 1); it was thus only resected when invaded by the tumor or unintentionally injured during the operation.

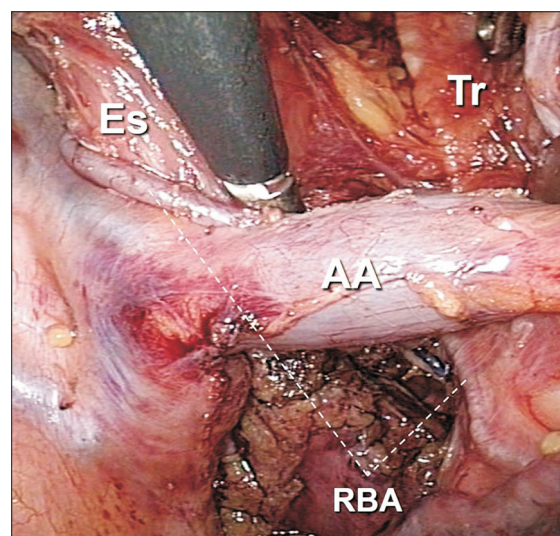During the study period, these procedures were per-

Fig. 1. The azygos arch (AA) was preserved during video-assisted thoracoscopic esophagectomy. The right bronchial artery (RBA) was also left intact. Es, esophagus; Tr, trachea.

formed by the same surgical team and thus remained consistent except for the AAP process. The amount of intraoperative blood loss was estimated by quantifying absorption in the surgical gauze and collection in the suction bottle. To precisely measure hemorrhagic volume in the gauze, we adopted the gravimetric method (i.e., weighing the gauze before and after the procedure). Postoperative complications were defined as those of grade III or greater severity, according to the Clavien-Dindo classification [22].

Statistical analysis

Continuous variables were compared using the Wilcoxon rank-sum test. Categorical variables were compared using the Pearson chi-square test. Simple linear regression analysis was performed to evaluate the correlations between continuous variables and intraoperative blood loss. Multiple linear regression incorporating the variables that showed a univariate association with blood loss with a p-value <0.15 was conducted to extract independent predictors. The p-values were all 2-sided, and p-values <0.05 were considered to indicate statistical significance. All statistical analyses were carried out using JMP Pro ver. 15.1.0 (SAS Institute, Cary, NC, USA).

Results

Associations between clinicopathological/surgical factors and bleeding amount

The median intraoperative blood loss volume was 225 mL (interquartile range [IQR], 126–380 mL). The relationships between baseline demographics and the intraoperative blood loss volume in all 168 patients are presented in Table 1. Blood loss was significantly higher in male patients than in female patients (p=0.013). Tumor-related factors such as muscular invasion, nodal metastasis, lymphatic involvement, and venous involvement were not significantly associated with the amount of blood loss. Neither preoperative chemotherapy nor radiotherapy showed a significant relationship with the blood loss volume. As regards operative factors, the open abdominal approach (p<0.001), thoracic duct resection (p=0.014), and azygos arch division (p<0.001) were significantly correlated with larger blood loss volume. There was no significant association between intraoperative blood loss and postoperative complications.

Simple linear regression analysis for intraoperative blood loss

Three continuous variables—body mass index (BMI), tumor size, and operation time—were also examined by simple linear regression analysis for possible associations with estimated blood loss (Table 2). BMI (p=0.003) and operation time (p<0.001) were positively correlated with the amount of intraoperative blood loss.

Multiple linear regression analysis

Table 3 shows the results of subsequent multiple linear regression for estimated blood loss involving 7 factors. Of these, 4 factors were identified as independent predictors of hemorrhagic volume: operative duration (p<0.001), an abdominal approach (p=0.003), azygos arch division (p=0.005), and BMI (p=0.014). Sex, preoperative chemotherapy, and thoracic duct resection were not independent predictors of blood loss during surgery.

Discussion

We retrospectively analyzed clinicopathological/surgical factors in 168 EC patients to identify associations with the amount of blood lost during VATS esophagectomy. We demonstrated that operation-related factors such as duration of the surgery, azygos arch division, and open laparotomy showed strong correlations with increased blood loss amount, as well as BMI. Although MIE may reduce the incidence of major complications without compromising long-term outcomes [23], minimization of the surgical risk remains a clinical challenge [2]. In this context, our results provide useful reference data.

A previous study suggested that BMI significantly influenced blood loss during esophagectomy for EC [24], although there is still no consensus regarding the role of BMI [25]. As for operation-related factors, the relationship between laparoscopic abdominal procedures and reduced blood loss demonstrated herein is quite plausible, and is supported by several lines of prospectively obtained evidence indicating the superiority of laparoscopic gastrectomy for reducing intraoperative hemorrhage [26,27]. To the best of our knowledge, however, there are no published data demonstrating the positive impact of AAP on surgical blood loss. Therefore, the finding that AAP was independently correlated with decreased blood loss might be the major finding of the present study. Clinicopathological factors such as T category, N category, or preoperative

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Table 1. Associations between clinicopathological/surgical factors and intraoperative blood loss in 168 patients

Variable	No. of patients	Intraoperative blood loss (mL)	p-value
Total	168	225 (126–380)	
Age at surgery			0.85
≤65 yr	72	259 (114–410)	
>65 yr	96	223 (130–370)	
Sex			0.013[*]
Male	141	265 (133–393)	
Female	27	160 (100–300)	
Tumor location			0.16
Upper third	26	173 (108–316)	
Middle third	85	268 (135–410)	
Lower third	57	225 (120–369)	
Histology			0.47
Squamous cell carcinoma	158	224 (129–371)	
Adenocarcinoma	10	363 (106–502)	
pT category			0.51
≤T1b	94	219 (125–371)	
≥T2	74	268 (129–401)	
pN category			0.21
N0	86	205 (125–353)	
≥N1	82	274 (135–410)	
Lymphatic involvement			0.62
Absent	97	222 (128–368)	
Present	71	260 (123–412)	
Venous involvement			0.65
Absent	75	223 (130–390)	
Present	93	258 (125–378)	
Preoperative chemotherapy			0.12
Absent	78	191 (112–374)	
Present	90	269 (139–393)	
Preoperative irradiation			0.51
Absent	153	239 (130–374)	
Present	15	154 (80–460)	
Three-field nodal dissection			0.18
No	45	175 (108–379)	
Yes	123	260 (135–381)	
Abdominal approach			<0.001[*]
Laparoscopic	117	191 (112–334)	
Open	51	356 (175–504)	
Esophageal replacement			0.69
Gastric conduit	115	222 (125–390)	
Other	53	265 (128–372)	
Reconstruction route			0.85
Retrosternal	159	239 (125–381)	
Posterior mediastinal	9	200 (105–456)	
Thoracic duct resection			0.014[*]
No	58	158 (100–368)	
Yes	110	274 (152–393)	
Azygos arch preservation			<0.001[*]
No	118	280 (144–416)	
Yes	50	164 (94–300)	
Right bronchial artery resection			0.54
No	137	260 (128–378)	
Yes	31	176 (100–408)	
Postoperative complications			0.29
Absent	128	223 (126–369)	
Present	40	303 (126–391)	

Values are presented as median (interquartile range).
[*]p<0.05.

Table 2. Simple linear regression analysis of associations with intraoperative blood loss

Variable	R^2	Beta	Coefficient	95% CI	SE	p-value
Body mass index (kg/m^2)	0.051	0.23	17.7	6.0 to 29.4	5.9	0.003[*]
Tumor size (mm)	0.0007	-0.03	-0.24	-1.6 to 1.2	0.71	0.74
Operative duration (min)	0.15	0.39	1.4	0.9 to 2.0	0.27	<0.001[*]

CI, confidence interval; SE, standard error.
[*]p<0.05.

Table 3. Multiple linear regression analysis of associations with intraoperative blood loss

Variable[a]	Beta	Coefficient	95% CI	SE	p-value
Male sex	0.12	41.0	-4.3 to 86.2	22.9	0.076
Body mass index (kg/m^2)	0.17	13.5	2.8 to 24.1	5.4	0.014[*]
Preoperative chemotherapy	0.08	19.8	-18.6 to 59.5	19.8	0.30
Open abdominal approach	0.20	54.5	18.4 to 90.5	18.3	0.003[*]
Thoracic duct resection	-0.03	-22.7	-52.3 to 37.5	22.7	0.74
Azygos arch division	0.21	56.8	17.4 to 96.2	19.9	0.005[*]
Operative duration (min)	0.34	1.3	0.8 to 1.8	0.25	<0.001[*]

CI, confidence interval; SE, standard error.
[*]p<0.05. [a]R^2=0.31.

therapy could be confounding factors for azygos arch transection. In our data, however, no significant relationships were confirmed between these factors and AAP (Supplementary Table 1).

AAP during thoracic esophagectomy is an uncommon technique that has been described in only a few publications to date [21,28]. Whether AAP is clinically justified was rarely discussed until the recent study by Fujiwara et al. [29], who comparatively analyzed the relationship between surgical outcomes and AAP in 119 patients undergoing MIE for EC and, interestingly, suggested that the achievement of AAP during thoracoscopic esophagectomy might enhance post-surgical urinary output. They also provided data on perioperative blood loss, which did not differ significantly between patients with and those without AAP, thus apparently contradicting our present results. This discrepancy must be carefully interpreted, however, because their sample size was smaller and the operative procedures were entirely different from ours.

The reasons why AAP was independently correlated with blood loss volume are difficult to explain because we still lack clinical evidence. One possible interpretation is that separation of the azygos system, a major drainage pathway for the portosystemic collateral circulation [30], impacts patients' congenital conditions, alters intraoperative circulation, and raises venous pressure, thereby exacerbating intraoperative bleeding. Nevertheless, these possibilities are speculative, because congenital status represented by a quantification of body weight gain on the first postoperative day did not appear to distinguish between the AAP and non-AAP groups (median, 6.7% [IQR, 5.0%–8.0%] versus median, 6.2% [IQR, 5.1%–7.4%]; p=0.16). Another possibility is that the superiority of AAP for reducing blood loss might have paralleled the time-dependent learning curve of the surgical team performing VATS esophagectomy, as AAP was conducted in the latter part of the study period. However, blood loss before and after the introduction of the AAP technique did not differ significantly in non-AAP cases (data not shown). We therefore speculate that other mechanisms underlie the relationship between blood loss and AAP, the identification of which will require additional experiments and prospective studies with larger numbers of subjects.

We should also pay attention to whether AAP influences surgical factors other than intraoperative blood loss. According to our data, resection of the right bronchial artery was significantly less frequent in patients with AAP (2/50 versus 29/118, p=0.002) and the duration of surgery was not prolonged in cases undergoing AAP (median, 588 minutes [IQR, 524–630 minutes] versus median, 584 minutes [IQR, 541–627 minutes]; p=0.76). Of note, however, the number of lymph nodes retrieved at the left recurrent nerve nodal station (106recL) and the left tracheobronchial nodal station (106tbL) differed significantly between patients with versus without the AAP procedure (median, 2.5 [IQR, 1–5] versus median, 5 [IQR, 3–8]; p<0.001). Although sufficiently long-term outcomes were not obtained in our cohort due to the short postoperative follow-up period,

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surgeons should keep in mind that AAP might be associated with oncological compromise as regards mediastinal nodal clearance.

The limitations of the present study include its retrospective nature and inherent selection bias with respect to the surgical procedure. Moreover, this was a single-institution study. However, the study population was originally derived from a cohort consistently treated by the same surgical team, under a shared philosophy, at a tertiary center highly experienced with esophageal surgery. Further multicenter validation is needed to confirm the current observations and obtain more concrete results.

In conclusion, surgical factors such as longer operative duration, open laparotomy, and azygos arch division were found to be independent predictors of increased blood loss during VATS esophagectomy for EC. Laparoscopic abdominal procedures are potentially a less invasive option than open procedures for decreasing intraoperative hemorrhage. AAP may also contribute to reducing the amount of bleeding during surgery, but might carry a risk of compromising oncological radicality.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Supplementary materials

Supplementary materials can be found via https://doi.org/10.5090/jcs.21.047. **Supplementary Table 1**. Associations between clinicopathological factors and azygos arch preservation.

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