PERIOPERATIVE TRANSFUSIONS FOR GASTROESOPHAGEAL CANCERS: RISK FACTORS AND SHORT- AND LONG-TERM OUTCOMES

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April 2020

A thesis submitted to McGill University in partial fulfillment of

the requirements of the degree of MSc in Experimental Surgery: Surgical Innovation

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ABSTRACT

Background

Perioperative blood transfusions have been associated with elevated postoperative morbidity for numerous surgical procedures and may be linked to poorer oncologic outcomes. However, this issue is understudied among patients with upper gastrointestinal malignancies. The objective of this study was to clarify the risk factors for and impact of perioperative blood transfusions on quality of life, surgical and oncologic outcomes among patients undergoing gastric and esophageal resections for cancer.

Methods

All patients undergoing curative-intent resections for gastroesophageal cancer between 2010-2018 were identified from a prospectively collected database. Perioperative blood transfusion was defined as red cell transfusion during surgery, 24 hours preoperatively and during the postoperative period. Baseline patient and tumour characteristics, neoadjuvant treatment, surgical procedure and approach, operative outcomes, long-term oncologic outcomes and quality of life score using the Functional Assessment of Cancer Therapy–Esophagus questionnaire at baseline and each follow-up visit were compared between transfused and non-transfused groups. Mann-Whitney U, Fisher Exact and χ^2 tests were used for univariate analysis. Multivariate regression analysis was performed to identify independent risk factors for transfusion and differences in oncologic outcomes. Results are presented as odds ratio [95% confidence interval].

Results

Of 766 gastric and esophageal resections performed over the study period, 435 patients met inclusion criteria [334 (77%) men; age 67 [59-75] years]. Tumour stage (American Joint Committee on Cancer 8th edition) was: 0-I in 60 (14%); II-III in 285 (66%); IV in 10 (2%), majority being adenocarcinoma: 390 (90%). Procedures in order of frequency were Ivor Lewis esophagectomy, subtotal gastrectomy, left thoracoabdominal esophagogastrectomy or extended total gastrectomy, total gastrectomy, McKeown esophagectomy, transhiatal distal esophagectomy and complex esophagectomy (modified radical cervical lymphadenectomy, pharyngolaryngoesophactomy and/or colon interposition). Perioperative transfusions occurred in 184 (42%) of cases. Moderate to severe anemia on day of surgery (6.208 [3.342-11.530]), blood loss above 400 mL (4.878 [2.657-8.954]), female sex (2.827 [1.425-5.608]), open approach (4.048 [1.724-9.504]) and prolonged operative time (1.008 [1.002-1.014]) emerged as independent risk factors for transfusions on multivariate analysis. Factors found to be independently associated with overall survival were tumour stage (T4, N2-N3), major (Clavien-Dindo≥3) complications, tumour size>3 cm and procedure type. Transfusions did not independently impact overall survival, disease-free survival or quality of life scores.

Conclusions

Perioperative red cell transfusions were associated with increased operative complexity and postoperative morbidity but did not impact long-term oncologic outcomes or quality of life among patients undergoing curative-intent surgery for gastroesophageal

cancer. Physicians should not be biased against perioperative red cell transfusion, when needed, for fear of impacting short or long-term outcomes.

ABSTRAIT

Contexte

Les transfusions sanguines périopératoires ont été associées à une morbidité postopératoire élevée pour de nombreuses procédures chirurgicales et peuvent être liées à de moins bons résultats oncologiques. Cependant, ce problème est sous-étudié chez les patients atteints de tumeurs malignes gastro-intestinales supérieures. L'objectif de cette étude était de clarifier les facteurs de risque et l'impact des transfusions sanguines périopératoires sur la qualité de vie, les résultats chirurgicaux et oncologiques chez les patients subissant une résection gastrique et œsophagienne pour cancer.

Les méthodes

Tous les patients subissant une résection à visée curative pour un cancer gastro-œsophagien entre 2010 et 2018 ont été identifiés à partir d'une base de données collectée de manière prospective. La transfusion sanguine périopératoire était définie comme une transfusion de globules rouges pendant la chirurgie, 24 heures en préopératoire et pendant la période postopératoire. Caractéristiques initiales du patient et de la tumeur, traitement néoadjuvant, procédure et approche chirurgicale, résultats opératoires, résultats oncologiques à long terme et score de qualité de vie à l'aide du questionnaire d'évaluation fonctionnelle de la thérapie anticancéreuse – œsophage au départ et chaque visite de suivi a été comparée entre transfusée et groupes non transfusés. Les tests Mann-Whitney U, Fisher Exact et $\chi 2$ ont été utilisés pour l'analyse univariée. Une analyse de régression multivariée a été réalisée pour identifier les facteurs

de risque indépendants de transfusion et les différences de résultats oncologiques. Les résultats sont présentés sous forme de rapport de cotes [intervalle de confiance à 95%].

Résultats

Sur 766 résections gastriques et œsophagiennes réalisées au cours de la période d'étude, 435 patients répondaient aux critères d'inclusion [334 (77%) hommes; 67 ans [59-75] ans]. Le stade tumoral (American Joint Committee on Cancer 8th edition) était: 0-I sur 60 (14%); II-III dans 285 (66%); IV sur 10 (2%), la majorité étant des adénocarcinomes: 390 (90%). Les procédures par ordre de fréquence étaient l'œsophagectomie Ivor Lewis, la gastrectomie subtotale, l'œsophagogastrectomie thoracoabdominale gauche ou la gastrectomie totale étendue, la gastrectomie totale, l'œsophagectomie McKeown, l'œsophagectomie distale transhiatale et l'œsophagectomie complexe (lymphadénectomie cervicale radicale modifiée, inter-adénectomie cervicale modifiée, pharyngolaryngo-atophagectomie ou colonophagectomie). Des transfusions périopératoires sont survenues dans 184 (42%) des cas. Anémie modérée à sévère le jour de la chirurgie (6.208 [3.342-11.530]), perte de sang supérieure à 400 ml (4.878 [2.657-8.954]), sexe féminin (2.827 [1.425-5.608]), approche ouverte (4.048 [1.724-9.504]) et un temps opératoire prolongé (1,008 [1,002-1,014]) sont apparus comme des facteurs de risque indépendants pour les transfusions dans l'analyse multivariée. Les facteurs associés indépendamment à la survie globale étaient le stade tumoral (T4, N2-N3), les complications majeures (Clavien-Dindo≥3), la taille de la tumeur> 3 cm et le type de procédure. Les transfusions n'ont pas eu d'impact indépendant sur la survie globale, la survie sans maladie ou les scores de qualité de vie.

Conclusions

Les transfusions de globules rouges périopératoires ont été associées à une complexité opératoire accrue et à une morbidité postopératoire, mais n'ont pas eu d'incidence sur les résultats oncologiques à long terme ou la qualité de vie chez les patients subissant une chirurgie à but curatif pour un cancer gastro-œsophagien. Les médecins ne devraient pas avoir un parti pris contre la transfusion de globules rouges périopératoire, si nécessaire, de peur d'avoir un impact sur les résultats à court ou à long terme.

ACKNOWLEDGEMENTS

I would like to thank all administrative, nursing and surgical staff in the Division of Thoracic and Upper Gastrointestinal Surgery at the Montreal General Hospital for making this research possible. It could not have been done without my supervisor, Dr. Carmen Mueller, who provided invaluable guidance and funded all research expenses. She was always available 24/7 if I had any questions or concerns and provided opportunity to work on extra projects with Dr. Jonathan Cools-Lartigue and Dr. Lorenzo Ferri, which have been helpful in preparation for my thesis. In addition, I am grateful for the office area that was provided for data collection, a clinical research coordinator (Aya Siblini) who assisted with ethics approval and Emma Lee for answering any questions I had about our electronic medical records system. I am also thankful to Lavaughn Lashley (archivist) and her team for providing paper charts. Quality of life data could not have been acquired without the help of Samantha Lancione and Sabrina Sacco, who administered questionnaires to patients in person and over the phone. I am grateful to Pepa Kaneva for her assistance with multivariate analysis, which has been invaluable in reaching our conclusion. I would also like to thank Dr. Lawrence Lee and Dr. Louis-Nicolas Veilleux (chairperson) who provided guidance for thesis preparation. I am thankful to our administrative support staff (Angela Alston, Michelina Frenza, Zelda Mackay, Lina Sobhi Abdrabo, Jessica Mancuso and Christine Cummings) for creating a cheerful atmosphere. Finally, I am eternally grateful to my mother, Rama Kammili, for providing boundless emotional and financial support for my education.

CONTRIBUTION OF AUTHORS

Pepa Kaneva

Pepa assisted with all multivariate analyses for this study.

Lawrence Lee

Dr. Lee assisted with the conception of this study and provided constructive criticism of results.

Jonathan Cools-Lartigue

Dr. Cools performed some surgeries for our study population and provided clinical knowledge and guidance as needed.

Lorenzo E. Ferri

Dr. Ferri performed majority of the surgeries for our study population, provided feedback for this project and revised the abstract for conference submission.

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This project was conceptualized by Dr. Mueller and she revised my thesis critically along with the abstract we submitted for this project. She performed surgeries in the study population, assisted with some data collection and analysis and ensured the statistical methodology had clinical significance.

INTRODUCTION

Rationale and Objectives

Patients with cancer in the upper gastrointestinal tract (esophageal and gastric cancer) have a high prevalence of anemia. One third of preoperative patients are anemic and the prevalence can rise to 90% depending on the underlying cancer, disease stage and definition of anemia.[1-15] Direct causes of anemia include bleeding from the cancerous tissue and indirect causes include cancer-related anemia.[1, 4, 5, 7, 8, 10, 16] Other causes of anemia include kidney failure, abnormal hemoglobin structure and vitamin deficiencies.[1, 4, 7, 8, 10, 13, 17, 18] The latter can occur in patients with bulky tumours that obstruct the passage of food.[19] Receiving neoadjuvant chemotherapy makes patients more susceptible to anemia as well due to bone marrow suppression during treatment.[2, 13, 14, 20-22]

Preoperative anemia has been shown to increase the risk of postoperative complications and blood transfusion among patients undergoing major surgery.[10, 12, 23-28] Surgery increases metabolic demands of the patient, similar to exercise, so anemia can be associated with reduced fitness for surgery as anemia is associated with lower exertional oxygen uptake and impaired exercise performance.[1] Causality between anemia and morbidity has not been directly proven, although increased morbidity and mortality was observed in most surgical specialties.[1, 4, 5, 12, 25, 26, 28-33] Current evidence suggests that treating anemia with transfusions, not the anemia itself, is associated with increased mortality.[2, 34]

Patients who undergo surgery for gastric and esophageal cancer frequently require transfusions, which are associated with worse prognosis.[5, 10, 18, 31, 35, 36] The negative effects caused by transfusion are thought to be due to transfusion-related immunomodulation; allogenic red blood cell (pRBC) transfusion reduces the activity of natural killer cells and T lymphocytes.[15, 31, 37-39] These cells are required to prevent dissemination of circulating and quiescent cancer cells and are also important for resistance to infections.[31, 40] Perioperative pRBC transfusion is associated with fever, increased length of stay, cost, mortality, infection and organ injury.[1, 2, 4, 5, 8, 12, 15, 18, 24-26, 28, 31-33, 35, 37, 41-48] A dose-dependent relationship between volume of blood transfused and prognosis is not observed.[5, 41, 42] Also, no significant differences in survival exist between the intraoperative and postoperative transfusion groups or the frequency of administration.[5, 35, 41] Furthermore, transfusions increase cancer recurrence and risk of developing new tumours.[15, 31, 37-39, 45-47, 49] Consequently, several studies have questioned whether pRBC transfusion is the most appropriate solution for preoperative anemia since it has been associated with decreased overall survival.[1, 4, 5, 18, 41, 49, 50]

There is insufficient data explaining the role of perioperative blood transfusions on quality of life, surgical and oncological outcomes for esophageal and gastric cancer resections. Also, most data are from Asia and Europe in other surgical specialties where they do not evaluate the risk factors for perioperative pRBC transfusions and their impact on quality of life, surgical and oncological outcomes for upper gastrointestinal cancers. Therefore, the objective of this study was to determine the risk factors for and impact of perioperative pRBC transfusions on surgical and oncological outcomes and quality of life

for patients undergoing gastroesophagectomy for gastric and esophageal cancers at a high volume North American specialized referral centre.

Literature Review

Epidemiology

Esophageal cancer is the sixth most common cancer worldwide and a significant cause of morbidity and mortality.[20, 31, 51] Squamous cell carcinoma (SCC) is the most prevalent, but its incidence and histology vary globally; SCC predominates in the "Asian esophageal cancer belt" extending from northeast China to the Middle East.[52, 53] The incidence of SCC increases with age, peaking in the seven decade of life.[52] In developed countries such as Australia, France and United States, adenocarcinoma (ADC) predominates.[52, 54] ADC is more common in men than women and its incidence rises with age.[52]

Gastric cancer is the fourth most commonly diagnosed cancer and the second most common cause of cancer mortality worldwide.[5, 17, 55] The case-fatality ratio of gastric cancer is higher than that of other common malignancies such as breast, colon and prostate cancers.[56] Highest incidence is documented in Eastern Asia, Eastern Europe and South America while North America and Africa show the lowest recorded rates.[56-58] Incidence has been shown to increase with age, peaking at 60-80 years.[59] The intestinal type is more common than the diffuse type, which is more often seen in female and young individuals.[60, 61] Furthermore, people migrating from high incidence areas (e.g. Japan) to low incidence regions (e.g. United States) have reduced gastric cancer risk.[58, 62]

Patients with gastroesophageal (GE) cancers have a high prevalence of anemia.[63] Anemia is prevalent in 30% of patients with esophageal cancer and 30-90% of patients with gastric cancer are anemic at diagnosis.[6, 63, 64] Up to 60% of patients have perioperative anemia, most of which require red cell transfusions.[5] Transfusion rates vary from 18% to 84% for GE cancers.[2, 5, 6, 31, 37, 41, 42, 50, 65-69]

Pathophysiology

Squamous cell carcinoma

Squamous cell carcinoma occurs in the middle and lower esophagus, with major risk factors being smoking and chewing tobacco and consuming alcohol.[70, 71] Combined consumption has a synergistic effect that increases the relative risk of SCC.[52] Alcohol damages the cellular DNA by decreasing metabolic activity in cells, reducing the function of detoxification while promoting oxidation.[72] Since alcohol is a fat-soluble solvent, hazardous tobacco carcinogens such as aromatic amines, nitrosamines, polycyclic aromatic hydrocarbons, aldehydes and phenols penetrate the esophageal epithelium easily.[52] Other carcinogens including nitrosamines found in preserved fish and salted vegetables have been linked to inflammation of the squamous epithelium, leading to dysplasia and malignant changes *in situ.*[73]

Adenocarcinoma

Adenocarcinoma of the esophagus has a direct link with gastroesophageal reflux disease (GERD) and primarily occurs in the distal esophagus and heterotopic gastric mucosa.[71, 74] Prolonged GERD progresses to Barrett's esophagus (BE) where the normal

stratified squamous epithelium is replaced by columnar epithelium due to chronic reflux of gastric acid and bile at the gastroesophageal junction.[52, 71, 75] Patients with BE are 50-100 times more likely to develop adenocarcinoma.[73] Another risk factor is obesity, especially abdominal-centered fat distribution.[52, 71] Hypertrophied adipocytes and inflammatory cells in fat deposits induce low-grade inflammation and promote tumour development by releasing adipokines and cytokines.[76] In this tumour microenvironment, adipocytes supply energy and support tumour growth and progression.[77]

Gastric adenocarcinoma development is a multistep and multifactorial process.[55] Tumours in the gastroesophageal junction (GEJ) involving the gastric cardia have shared histologic features and immunophenotypes between the metaplastic columnar epithelium-lined distal esophageal mucosa secondary to reflux disease and inflamed gastric cardiac mucosa due to *Helicobacter pylori* (*H. pylori*) infection.[78, 79] Intestinal and diffuse type adenocarcinoma are the two major histological subtypes.[80] The intestinal type is associated with intestinal metaplasia and *H. pylori* infection.[81, 82] Human epidermal growth factor receptor (HER2) is often overexpressed in intestinal ADC and located more often in the proximal stomach (gastric cardia) and GEJ than in the remaining stomach.[83] In addition, HER2 positive GEJ and gastric carcinomas are relatively homogenous and rarely show significant modification from primary site to metastatic foci.[83] *H. pylori* effects early stages of gastric carcinogenesis; chronic gastritis is induced by the formation of free radicals by inflammatory cells, production of nitric oxide, nitrates and nitrosamines by macrophages and increased cell turnover.[84] The diffuse type is commonly associated with genetic abnormalities.[55] A germline mutation in the tumour suppressor gene E-cadherin

or CDH1 results in the inactivation of E-caderin, methylation and loss of heterozygosity that triggers the development of gastric cancer.[85, 86] Linitis plastica describes malignancies where most of the gastric wall is involved by infiltrating tumour cells.[55] In summary, gastric cancer has a multifactorial etiology (diet, lifestyle, genetic and socioeconomic), but the majority are attributed to *H. pylori* infection.[59]

Rare cancers

Rare tumours can be biphenotypic.[71] When tumours are composed with intimate admixture of squamous and mucinous elements, they are named mucoepidermoid carcinoma while tumours composed of two separate squamous and mucinous elements are termed adenosquamous carcinoma.[71]

Anemia

Patients with GE cancers develop anemia due to various causes. Radiation and platinum-based chemotherapy, the cornerstone of treatment for GE cancers, frequently leads to anemia.[63, 87] Voelter *et al.* demonstrated that more than 80% of patients experience a decrease in hemoglobin during chemotherapy by more than 2 g/dL (20 g/L).[68] This is a result of myelotoxicity of platinum-based regimens and the severity of anemia depends on the cumulative dosage of chemotherapy.[87-89] Furthermore, anemia of chronic disease results from shortened red cell survival, failure of bone marrow to increase erythropoiesis to meet the demand and to repair the deficiency (i.e. hypoproliferative state) and failure of the bone marrow to release iron from the senescent red cells that were phagocytosed by the bone marrow macrophages (i.e. defective iron

utilization).[13, 90] Cancer-related anemia is similar; the hypoproliferative state observed in cancer-associated anemia is either related to decreased erythropoietin production or impaired bone marrow response to erythropoietin.[13] Moreover, cytokines liberated in cancer patients could inhibit erythropoietin secretion and its responsiveness to the marrow erythroid progenitors.[13] Tumour-associated bleeding contributes to anemia as well due to bleeding associated with ulcerated tumours and iatrogenic blood loss, either during surgery or endoscopy.[91, 92] Finally, nutritional deficiencies including iron, folate, vitamin B12 and global malnutrition secondary to obstructive tumours can cause anemia.[19, 91, 92]

Diagnostic methods

Clinical TNM staging of cancer is essential for diagnosis and treatment planning.[52] Endoscopic ultrasound (EUS), computed tomography (CT) and ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) scans are utilized to accurately establish depth of tumour invasion (T stage). EUS is more accurate at differentiating between T1, T2 and T3 tumours and determining nodal involvement.[93, 94] CT is commonly used to rule out distant metastasis and FDG-PET is more accurate in detecting distant metastasis.[52, 95] Tumour histology can be determined from biopsy specimens and immunohistochemistry can be performed on biopsies and resections for HER2 status determination.[55, 71] Molecular testing applications include CDH1 gene testing for diffuse gastric carcinoma.[55] The distinction between early and advanced cancer is important to help decide if neoadjuvant therapy is warranted as it improves disease-free and overall survival compared to surgery alone.[96, 97]

Treatment modalities

Surgery

High grade dysplasia and early stage cancers can be treated definitively with endoscopic mucosal resection, endoscopic submucosal dissection or various types of esophagogastrectomy (transhiatal vs. transthoracic, open vs. minimally invasive).[98, 99]

Chemoradiotherapy

For locally advanced cancer such as T3N1, chemotherapy or chemoradiotherapy is administered in the neoadjuvant and adjuvant setting.[52] Commonly used systemic chemotherapy regimens may include: paclitaxel + carboplatin or cisplatin + fluoropyrimidine dual agent regimens or most often: docetaxel or oxaliplatin + fluorouracil + cisplatin triplet therapy.[52, 100, 101] Radiation dosages used in conjunction with chemotherapy sensitizers usually ranges from 41.4-50.4 Gy.[102]

Red cell transfusions

Most treatment strategies exacerbate anemia; consequently, the majority of patients require intravenous administration of pRBC transfusions to relieve the symptoms of anemia such as fatigue and dyspnea.[92]

Immunomodulatory effect of transfusions

Both *in vitro* and *in vivo* evidence shows that allogenic transfusions alter the recipient's immune system, known as transfusion-related immunomodulation (TRIM), and their ability to respond to infections and tumour antigens.[44, 103, 104] However, TRIM

continues to be a debatable complication of transfusion.[46] TRIM is likely multifactorial and has been shown to be mediated by allogenic mononuclear cells, leukocyte-derived soluble mediators or soluble HLA peptides.[44] Consequently, leukoreduction of pre-storage red cell units is routine.[38]

Nevertheless, administration of leukoreduced pRBC triggers release of interleukin (IL)-6, IL-10 and tumour necrosis factor alpha (TNF-α), reduces lipopolysaccharide-induced release of TNF-α and induces regulatory T-cell (Treg) activation.[105-107] Treg cells co-express high levels of the IL-2 receptor-α ($CD25^{hi}$), inhibit IL-2 production and supress Th1 function via cluster of differentiation $(CD)4^{+}$ and $CD8^{+}$ cells.[38, 108, 109] Treg cell activation is antigen nonspecific; they can be activated by lipopolysaccharide and Toll-like receptor-4 pathway to become immunosuppressive.[110] Therefore, inflammation and immunosuppression can be encountered with administration of pRBC regardless of leukoreduction.[38] Along with residual leukocytes and biologically active cytokines, pRBC units also contain non-polar lipids and a mixture of pro-inflammatory lysophosphatidylcholines (LPCs); LPCs modulate the activity of natural killer (NK) and T cells, act as NK cell chemoattractant, induce dendritic cell maturation and stimulate the production of pro-inflammatory cytokines.[111-115] Prostaglandins and thromboxanes also accumulate in pRBCs.[116] The overall effect of these substances leads to immunosuppression and tumour-promoting action.[117-120]

Refaai and Blumberg summarize the effects of transfusion in the immune system as the following: decreased Th1 and increased Th2 cytokine production *in vitro*, reduced

responses in mixed lymphocyte culture, decreased proliferative response to mitogens or soluble antigens *in vitro* (thus causing impaired delayed-type hypersensitivity skin responses), increased CD8 T cells or suppressor function *in vitro*, decreased activity and quantity of NK cells *in vitro*, decreased CD4 helper T cells, decreased monocyte/macrophage function *in vitro* and *in vivo*, enhanced production of anti-idiotypic antibodies suppressive of mixed lymphocyte response *in vitro*, decreased cell-mediated cytotoxicity against target cells *in vitro*, humoral alloimmunization to cell-associated and soluble antigens and increased quantity and function of Treg cells.[44, 121]

In summary, gastroesophageal cancer patients are at high risk of anemia due to a multitude of cancer- and treatment-related factors. Anemia is often treated with red cell transfusions in this population, especially in the perioperative period of gastrectomy or esophagectomy for cancer. While necessary to preserve life during or after major surgery, red cell transfusions have been associated with increased morbidity, worse oncologic outcomes and decreased quality of life in studies that evaluated patients with other cancers. However, this is understudied among gastroesophageal cancer patients and the reasons for these associations remain unclear. Therefore, the purpose of this study was to assess the impact of perioperative red cell transfusions on operative, oncologic and quality of life outcomes among patients with gastroesophageal cancers.

METHODOLOGY

Study subjects

Patients who underwent surgery for gastroesophageal cancers from January 2010 to December 2018 were identified from prospectively collected databases managed by the Division of Thoracic and Upper Gastrointestinal Surgery (FileMaker Pro™ 7.0 version 2 © 2004 by Claris International) and perioperative services at the Montreal General Hospital (Centricity Opera version 5 © 2017 General Electric Company). Patients undergoing curative-intent surgery for gastric and esophageal cancers were included while palliative, prophylactic and benign resections, patients with presence of rare (non-ADC or SCC) cancers, other synchronous and/or prior cancers were excluded. Informed consent was provided by all patients for surgery and potential use of data for quality control and research purposes in an academic setting.

Data collection and classification

The primary outcome was overall and disease-free survival. Secondary outcomes included: patient and tumour characteristics, operative outcomes, complications, mortality and quality of life. All data were collected prospectively and verified with thorough review of paper and electronic medical records (vOACIS – version 7.5.0 patch 12B Open Architecture Clinical Information System by Telus Health). Ethics approval was obtained from the Research Ethics Board of McGill University Health Centre in Montreal, Canada.

Age-adjusted Charlson comorbidity index (CCI) was used to categorize comorbidities and age.[122-125] Any node positive disease, T3 and T4 were classified as

locally advanced cancer.[126, 127] Node negative and T1-2 stage tumours were classified as early stage cancer.[128] Anemia was categorized according to World Health Organization's cut-offs: mild (110 g/L to normal), moderate (80 g/L to 110 g/L) and severe anemia (less than 80 g/L).[129] All tumours were restaged according to the American Joint Committee on Cancer (AJCC) eighth edition.[130, 131] Post-operative complications were classified using Clavien–Dindo score (CDS).[132] Death certificates and Quebec cancer registry were used for dates of death to determine mortality. Functional Assessment of Cancer Therapy-Esophageal (FACT-E) questionnaires (see Appendix II) administered at every appointment were used to determine QoL scores (see Appendix III).[133]

Statistical analysis

Patients who received packed red blood cell transfusions intravenously were compared with those who did not in the perioperative period, defined as 24 hours before surgery, during surgery or within the postoperative hospitalization period.[5, 38, 41, 42, 134-137] The number of units were compared as well. Data were analyzed using Mann-Whitney U, Fisher-Exact, Kaplan-Meier, log rank and $\chi 2$ tests. Multiple logistic regression was used for determining independent risk factors for transfusions with the model being built using statistically significant factors identified on univariate analysis as well as clinically relevant parameters. Cox proportional hazards regression model was employed to determine variables independently predictive of overall and disease-free survival. Excel version 1908 from Microsoft® Office 2019 and SAS 9.4 by SAS Institute 2013 were utilized for statistical analysis. Data are presented as median [interquartile range]. A *p* value of less than 0.05 determined statistical significance.

RESEARCH FINDINGS

Patient Characteristics

Of a total 766 gastroesophageal resections performed between 2010-2018, 446 met inclusion criteria. Among those, 11 (2%) were excluded due to lack of transfusion data availability and 435 patients were included (Figure 1).

Of included patients, 184 (42%) received perioperative red cell transfusions versus 251 (58%) who did not; *p*=0.001 (Table 1). The rate of transfusions decreased from 50% to 40% over the study period (Figure 2). There was a male preponderance in both groups while the male to female ratio was well balanced (M: 334 (77%), F: 101 (23%); *p*=0.112). Patients were older (pRBC: 68 [60-76], no pRBC: 65 [59-73]; *p*=0.010) and had more severe comorbidities (CCI ≥5 points: pRBC: 108 (59%), no pRBC: 114 (45%); *p*=0.008) in the transfusion group. Patients who required transfusions had lower body mass index (pRBC: 25 ± 5 kg/m^2, no pRBC: 26 ± 5 kg/m^2; *p*=0.003).

A total of 270 (62%) GEJ, 125 (29%) gastric and 40 (9%) esophageal cancer patients were in the final cohort. Adenocarcinoma predominated in both groups (pRBC: 158 (86%), no pRBC: 232 (91%); *p*=0.026), followed by squamous cell carcinoma (pRBC: 26 (14%), no pRBC: 19 (8%); *p*=0.026), with a high proportion of poorly differentiated tumour cells in both groups. Presence of HER2 mutations did not vary by group. Clinical stage was higher in the transfusion group (AJCC stage III-IV: pRBC: 106 (57%), no pRBC: 111 (45%); *p*=0.002). Rates of neoadjuvant therapy (pRBC: 124 (67%), no pRBC: 160 (64%); *p*=0.570) and transfusions during workup and neoadjuvant therapy (pRBC: 0 [0-

2] units, no pRBC: 0 [0-1] units); p=0.342) did not vary among groups. Anemia was more prevalent in the transfusion group: hemoglobin at diagnosis (pRBC: 124 [108-138] g/L, no pRBC: 137 [119-148] g/L; p<0.001), preoperatively (pRBC: 109 [99-120] g/L, no pRBC: 126 [115-138] g/L; p<0.001) and on day of surgery (pRBC: 102 [89-113] g/L, no pRBC: 121 [115-132] g/L; p<0.001) was lower in the transfusion group. Five patients (3%) required pRBC transfusions preoperatively in the transfusion group. Coagulation parameters were comparable among groups. Post-operative care for all patients was undertaken by the dedicated Thoracic and Upper Gastrointestinal Surgery multidisciplinary care team (including specialized surgeons, nurses, dieticians and other support personnel) in accordance with the standardized enhanced recovery after surgery (ERAS) pathway developed by a dedicated committee of the McGill University Health Centre.[138, 139] Patient characteristics are presented in Table 1.

Figure 3 displays the trend of hemoglobin from diagnosis to treatment grouped by presence and absence of neoadjuvant therapy. While a measured drop in median hemoglobin was observed in those who received neoadjuvant therapy, no difference was observed in median hemoglobin between groups preoperatively and on day of surgery.

Operative outcomes

Ivor Lewis esophagectomy (187, 43%) was the most commonly performed procedure in this cohort, followed by: subtotal gastrectomy (84, 19%), left thoracoabdominal esophagogastrectomy or extended total gastrectomy (55, 13%), total gastrectomy (42, 10%), McKeown esophagectomy (35, 8%), transhiatal distal

esophagectomy (21, 5%) and complex esophagectomy (11, 3%). Transfusions were more prevalent in those who had surgery using the open approach (Table 2). Extended (D2) lymphadenectomy with skeletonization of the celiac vessels and proximal ligation of the left gastric artery was routinely performed in 395 (91%) of patients. Duration of surgery was comparable among groups while estimated blood loss was higher in the transfusion group (pRBC: 500 [250-750] mL, no pRBC: 250 [150-400] mL; $p<0.001$). Transfused patients received a median of 1 [0-2] packed cell units per patient intra-operatively and 1 [0-2] units post-operatively, with 38 (43%) of post-operative transfusions occurring in patients who had also received blood transfusions during surgery. Severe postoperative complications (Clavien-Dindo 3-4) (pRBC: 56 (30%), no pRBC: 37 (15%); $p<0.00001$) and 30-day mortality (pRBC: 14 (8%), no pRBC: 2 (1%); $p<0.001$) were higher in the transfusion group while the number of emergency room visits and readmissions were comparable between groups. Complications such as anastomotic leak, reintubation, surgical site infection and myocardial infarction were higher in those who received pRBC transfusions (Table 3).

Oncological outcomes

Tumours were larger in the transfusion group (pRBC: 4.3 ± 3.2 cm, no pRBC: 3.3 ± 2.4 cm; $p=0.003$) and had more lymph node metastasis (pRBC: 2 [0-7], no pRBC: 1 [0-3]; $p=0.031$). Total number of lymph nodes retrieved, lymphovascular and perineural invasion were comparable among groups. Pathological stage, positive margins and rates of pathologic complete response were similar between groups. However, tumours were more invasive (T4 pRBC: 34 (18%), no pRBC: 18 (7%); $p<0.001$) and had a higher lymph

node status (N3 pRBC: 45 (24%), no pRBC: 30 (12%); p<0.001) in the transfusion group. Oncological outcomes are presented in Table 4.

Quality of life

Patient-reported quality of life scores from FACT-E questionnaires are presented in Table 5. Overall quality of life scores were similar between groups at all timepoints from diagnosis to follow-up three years postoperatively: pre-neoadjuvant therapy: 114 [95-135]; preoperative visit: 122 [103-138]; first postoperative visit (around one month): 112 [97-128]; three months postoperative: 125 [110-141]; six months postoperative: 131 [102-141]; one year postoperative: 128 [113-152]; two years postoperative: 141 [128-153]; three years postoperative: 140 [124-159].

Long-term survival

Kaplan-Meier survival curves for transfused and non-transfused groups are depicted in Figure 4 for disease-free and overall survival. Those who did not receive perioperative pRBC transfusions had higher DFS and OS on univariate analysis. Figure 5 demonstrates an inverse relationship between survival and quantity of pRBC transfused for both DFS and OS.

Cox proportional hazard analysis for DFS (Table 6) demonstrated the following factors to independently influence DFS: neoadjuvant therapy, major (Clavien-Dindo≥3) complications and T4 or N1-N3 pathological stage negatively impacted disease-free

survival. The number of pRBC units transfused, age, sex, comorbidities, approach, procedure and tumour size did not influence DFS independently.

Table 7 depicts factors that were independently associated with OS: major complications, pathological T4 or N2-N3 stage and tumour size above 3 cm negatively impacted overall survival while gastrectomy was protective when compared to esophagectomy. Transfusions and pathological N1 stage did not independently impact disease-free or overall survival.

Risk factors for transfusion

Independent risk factors for perioperative pRBC transfusions (Table 8) were: female sex, moderate to severe anemia on day of surgery, operative blood loss above 400 mL, open surgical approach and prolonged operative time. Age, comorbidities, BMI, neoadjuvant therapy, procedure type, presence of locally advanced cancer and surgical approach (open vs. minimally invasive) were not independent risk factors for transfusion.

DISCUSSION

Summary of results

This study demonstrated that perioperative red blood cell transfusions can be administered safely for patients undergoing curative-intent surgery for gastroesophageal cancer without transfusions having an impact on quality of life or surgical and oncological outcomes. Independent risk factors for transfusion were anemia, blood loss, open approach, operative time and female sex. Independent factors influencing disease-free survival include neoadjuvant therapy, complications and tumour stage while factors independently impacting overall survival were cancer stage, tumour size, procedure and complications.

Baseline patient and tumour characteristics

As seen in numerous studies and our patient population, patients receiving transfusions tend to be older, thinner, anemic, suffer from many comorbidities and have greater tumour extension with node positive disease resulting in higher disease stage pre-treatment.[5, 31, 40, 42, 65] More extensive tumours tend to metastasize to lymph nodes, resulting in more node positive disease requiring neoadjuvant therapy in the transfusion group.[140] Furthermore, administration of neoadjuvant chemotherapy induces anemia, which is illustrated by the drop in hemoglobin shown in our data and other studies.[65, 68]

Relationship between perioperative transfusion and surgical outcomes

Patients who had surgeries under the open approach tended to bleed more, which correlated with a higher incidence of open surgery in the transfusion group in our analysis.

In addition, transfused patients experienced greater rates of post-operative complications and prolonged length of stay postoperatively. Similarly, many studies report poorer prognosis among surgical patients who received allogenic pRBC transfusions versus those who did not.[2] Higher rates of complications, increased blood loss, length of stay, mortality and overall survival are observed in transfusion groups.[2, 31, 65, 69, 141] This aligns with our results on univariate analysis. However, as demonstrated in our multivariate analysis, transfusions were not found to independently predict worse operative, oncologic or quality of life outcomes. Perioperative transfusions in this study were associated with increased surgical complexity, including increased blood loss, length of surgery and post-operative complications.

Short-term oncological outcomes

Patients requiring transfusions had larger, more extensive tumours and greater number of positive lymph nodes as seen in literature and our study.[5] Tumours larger than 4 cm and of advanced stage are ulcerated and usually manifest themselves in the form of digestive bleeding, which likely explains why patients in the transfusion group had larger tumours.[40, 142] Many authors theorize that tumour depth and size predict lymph node positivity, explaining the presence of more positive lymph nodes in the group with these tumour characteristics.[140, 143, 144]

Effect of perioperative transfusion on quality of life

Despite the differences in tumour stage, comorbidities, and surgical complexity observed among transfused and non-transfused patients in this cohort, quality of life at

all time points was similar. Sundaram *et al.* compared QoL between open and minimally invasive esophagectomy, where the latter group received fewer transfusions, and showed that QoL was comparable among groups.[67] This could be extrapolated as increased transfusions not impacting quality of life, which would align with our QoL results. In addition, our study indicates that QoL improved after neoadjuvant therapy and surgery, which is attributable to relieving symptoms associated with having an obstructive tumour and undergoing curative-intent surgery. Most GE cancer patients present with anemia or develop chemotherapy-induced anemia due to myelosuppression.[68] Such patients are administered transfusions if their hemoglobin levels are low, which in turn relieves the symptoms of anemia and improves their QoL.[87, 145, 146] Otherwise, cancer-related fatigue caused by anemia has a significant impact on patients' QoL.[63, 147] A clear relationship has been established between improvement in QoL scores and the postoperative interval.[148] The surgical procedure itself is a factor that worsens QoL, as seen by the drop in QoL scores in the first postoperative visit, and was also found to be significant in other studies.[148-151] The literature and our data report that improvement in QoL starts at 3 months postoperatively, becomes substantial after 6 months and completely recovers with resolution of symptoms associated with surgical sequelae between 12 and 24 months.[67, 148, 149, 151-154] Patients should be informed that quality of life will deteriorate short-term while recovering from surgery and that it will start improving substantially after 3 months, regardless of transfusion requirements.

Relationship between survival and transfusions

The relationship between perioperative blood transfusions and survival is controversial. Many studies have shown a significant deleterious effect on survival related to perioperative transfusions while some demonstrated similarity.[31, 42] Often, these studies have been limited by small sample sizes and use of univariate analysis alone, making interpretation of the true impact of transfusions challenging.[42, 65, 137, 141] Furthermore, large database studies are limited by lack of granularity of data regarding tumour stage, adjuvant therapy, surgical details, post-operative care and timing, quantity and reason for transfusions, limiting interpretation of the true impact of transfusions on outcomes. Kaneda *et al.* showed a significantly lower survival for patients in the transfused group and subgroup analysis illustrated a significant difference in the range of survival time for patients with stage I gastric cancer while Liu *et al.* showed worse outcomes in patients with stage III gastric cancer.[5, 141] However, their analysis had a small group of patients and only univariate analysis was employed.[42, 141] Differences in baseline patient and tumour characteristics must be adjusted for using multivariate regression analysis for accurate interpretation of these results.[137] Reeh *et al.* demonstrated that both DFS and OS were higher in the transfused group even on multivariate analysis.[31] However, these studies did not include some significant parameters in their multivariate model such as blood loss and hemoglobin level. Conversely, some studies showed no difference in transfused and non-transfused patients grouped by stage when multivariate analysis was utilized for simultaneous adjustment of all covariates.[40, 137, 142, 155] Moriguchi *et al.* showed no relationship between groups using univariate analysis grouped by stage for curative gastric cancer resections.[137] Bortul *et al*. illustrated that T and N stage were

associated with lower survival where the multivariate analysis showed that transfusions were not an independent variable.[155] These articles demonstrate that transfusions, even though they tend to be associated with decreased survival in some studies, do not independently impact survival when confounding variables are incorporated into multivariate analysis, which is in keeping with the findings we report in this analysis.

Disease-free survival

Disease free survival was lower in the transfused group in our univariate analysis, which mirrors other studies.[41, 42] However, this significant difference disappeared on multivariate analysis when covariates were taken into consideration. Furthermore, the quantity of transfusion did not correlate with survival as seen in a multicentre study.[41] Nevertheless, neoadjuvant therapy, major complications and pathological tumour stage independently influenced disease-free survival. This is consistent with other studies.[5, 31, 41, 136, 156, 157] Neoadjuvant therapy improves local tumour control, thus decreasing recurrence and consequently improving DFS. Rausei *et al.* determined that lymph node status is an independent prognostic factor and suggested that perioperative blood transfusions are a confounding factor more than a prognostic indicator, which is reiterated by our results.[136]

According to our results and those reported by others, age, sex, comorbidities and approach did not influence DFS independently.[31, 158, 159] Some studies have demonstrated that comorbidities have a negative effect on DFS.[159-161] Ribeiro *et al.* hypothesized this difference is a result of lower level of anti-tumour activity in patients with severe

comorbidities or biases of the physician in treatment planning and suggested close follow-up in patients with many comorbidities.[160] Meyerhardt *et al.* concluded that the higher risk of recurrence was attributed to hyperinsulinemia of diabetes, resulting in more rapid tumour progression since high levels of circulating insulin and other insulin-like growth factors promote cellular proliferation and affect apoptosis.[162-164] In contrast, some treatments for diabetes, particularly metformin and thiazolidinediones, have anti-neoplastic activity that slows cancer progression.[163, 165] Consequently, patients with diabetes can have lower relapse rates due to the favourable impact of metformin outweighing the unfavourable impact of diabetes itself.[166] This explains why Kanda *et al.* and our results showed that comorbidities did not influence DFS.[167]

Straatman *et al*. conducted a randomized controlled trial to illustrate that minimally invasive and open surgery have comparable DFS, mirroring our finding that approach does not influence DFS.[168] Other studies comparing type of procedure for esophagectomy and/or gastrectomy for cancer showed that the type of procedure does not impact disease-free survival, which mirrors ours findings.[169-171] A review by Soerjomataram *et al.* summarized that tumour size results in more lymph node metastasis and recurrence where they correlated tumour size with depth of invasion (T).[172] However, the size used in this study for describing tumours was the largest dimension (which could be the width, not necessarily the dept of tumour invasion), explaining why size does not impact DFS in our series. Our results conclude that perioperative transfusions do not independently impact disease-free survival and that other factors such as tumour stage and complications are more likely to impact DFS negatively.

Overall survival

In our study, overall survival was higher in those who did not receive perioperative transfusions, implying transfusions decrease survival when univariate analysis is used. This is consistent with other studies that also compared transfusion using univariate analysis.[18, 42, 65, 142] Intraoperative and postoperative transfusions were analyzed by Chang *et al.* to show that unnecessary blood transfusions should be avoided because they decreased overall survival in their cohort.[18] Lee *et al.* analyzed survival rates by the number of units transfused using Kaplan-Meier survival curves to show that increased quantity of transfusions result in worse survival.[65] This mirrors our results as well; however, we demonstrated that this difference disappears with multivariate analysis where transfusion does not influence overall survival when confounders are considered. Choi *et al.* performed a subgroup analysis and did not find any causal relationships between transfusion and prognosis, supporting our results.[142] Contrary to our findings, transfusions remained an independent prognostic factor for overall survival in some studies.[41, 65] This could be attributed to the variables used in their multivariate Cox regression analysis because they did not include some clinically important covariates such as complications, tumour size and type of procedure. The benefits of this single center review of prospectively followed patients is the depth of data available, allowing for improved analysis of possible confounding variables related to outcomes than those previously reported by analysis of large surgical databases. Our results showed that, as expected, procedure type, complications, cancer stage and tumour size impact OS while transfusions alone do not.

Risk factors impacting perioperative pRBC transfusions

Our results indicate that moderate to severe anemia, intraoperative blood loss greater than 400 mL, increased operative time and female sex are independent risk factors for perioperative transfusion. Likewise, low hemoglobin was one of the main predictors of transfusion in other studies.[4, 68, 173] Ojima *et al*. determined operative time and blood loss as a risk factor as well, but their cut-off was 1000 mL.[42] Bortul *et al.* suggest the primary goal should focus on minimizing operative blood loss.[155] Two benchmark studies showed that women tend to have a higher transfusion rate and volume, which can be explained by clinicians applying the same absolute transfusion thresholds irrespective of gender even though WHO's anemia cut-offs for women are lower.[174] In addition, no cut-off values or transfusion guidelines exist specifically for post-menopausal women.[174] Consequently, women undergo more liberal transfusions.[174] This explains why female sex was a risk factor for transfusion in our study as the majority of women in our cohort were of post-menopausal age. In conclusion, our results indicate transfusions themselves are not the driver of poor outcomes, but rather are associated with patients who are predisposed to anemia and blood loss from complex surgery.

Limitations

Limitations of this study include its retrospective nature. Although data was prospectively collected, the retrospective nature of the analysis limits conclusions to associations only. Nevertheless, the large patient cohort strengthens the validity of our findings. Additionally, this work was carried out in a single center, limiting the generalizability of our findings. Administration of adjuvant therapy was not evaluated,

which could be a confounder for some variables such as quality of life and long-term survival. In addition, selection bias was present as the decision to transfuse is subjective and some practitioners may have been more liberal with transfusions than others. All tumours were reclassified using AJCC's 8th edition while other studies predominantly used the 7th edition. This may cause difficulty in eliciting accurate comparisons between studies, but the eighth edition has been shown to be valid and will be employed in future studies.

CONCLUSION

Perioperative red blood cell transfusions are associated with elevated cancer stage, patient comorbidities, complex and prolonged surgery and post-operative complications, but are not an independent predictor of long-term oncologic or quality of life outcomes after gastroesophagectomy for cancer. Perioperative care physicians should not be biased against transfusion, when required, for fear of worsening long-term cancer-related outcomes.

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FIGURES AND TABLES

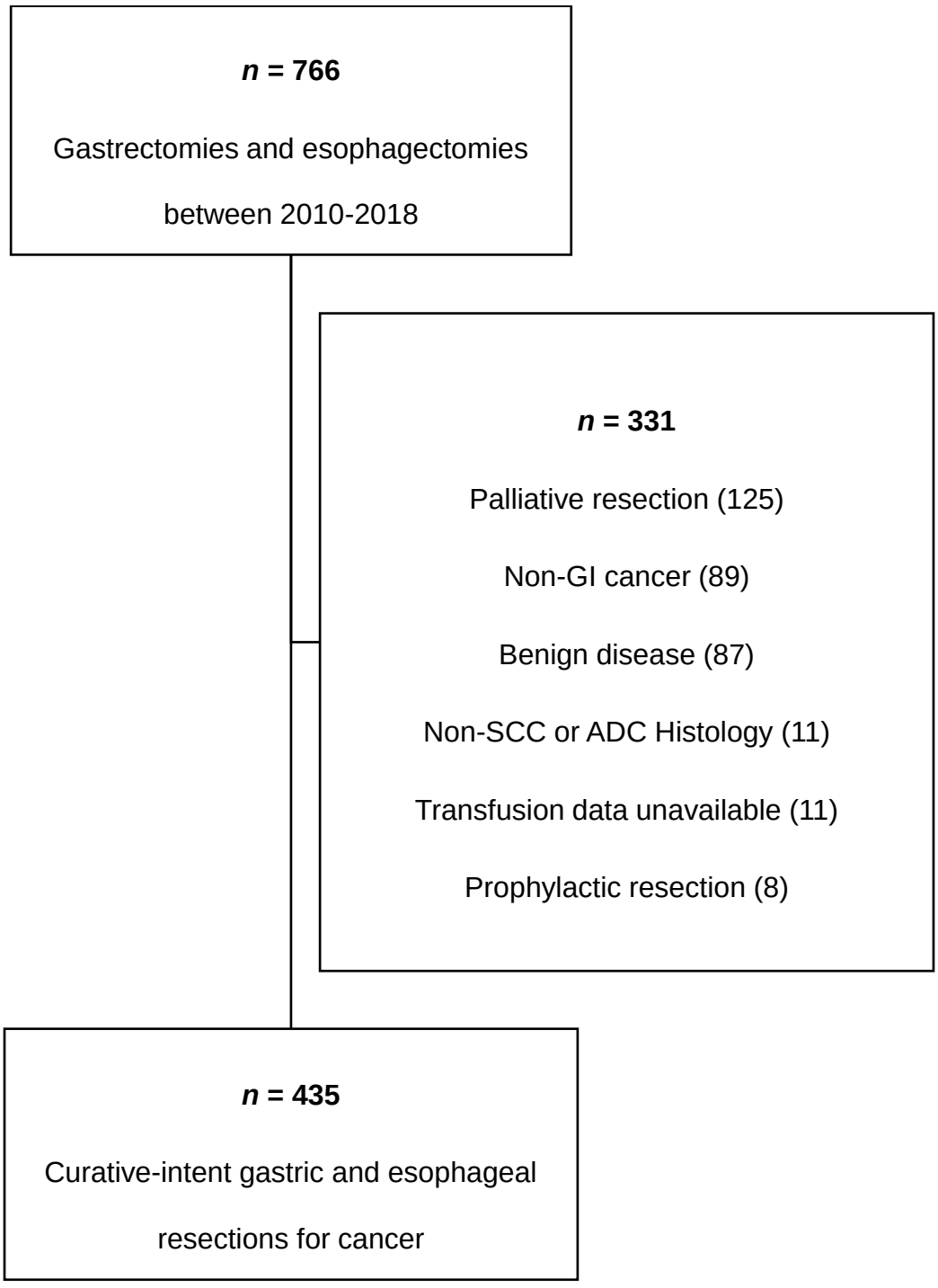

Figure 1. Flow diagram of inclusion and exclusion criteria

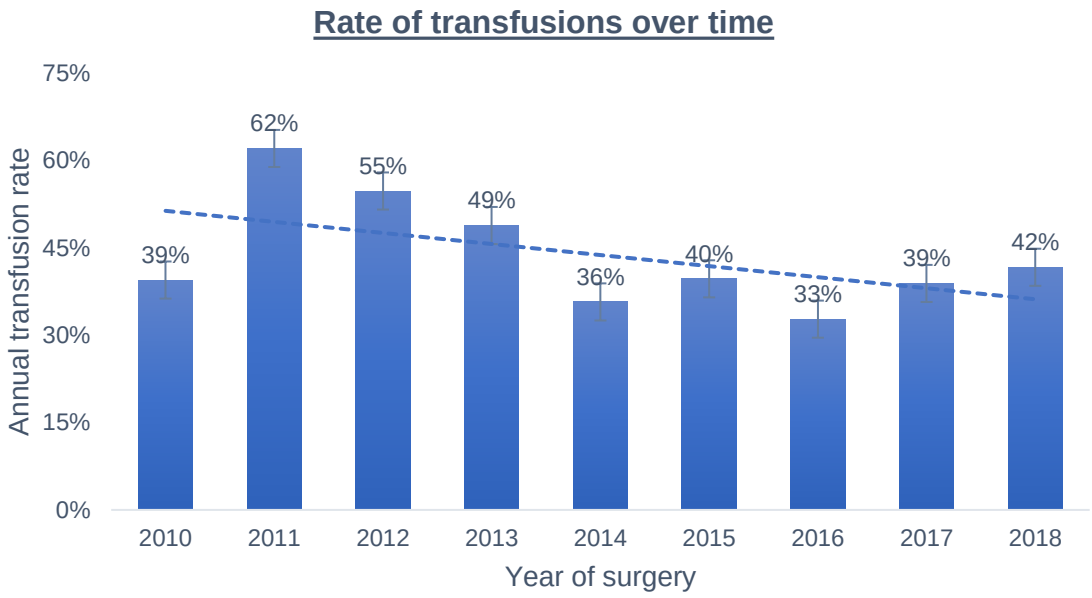

Figure 2. Percentage of packed red cell transfusions over time

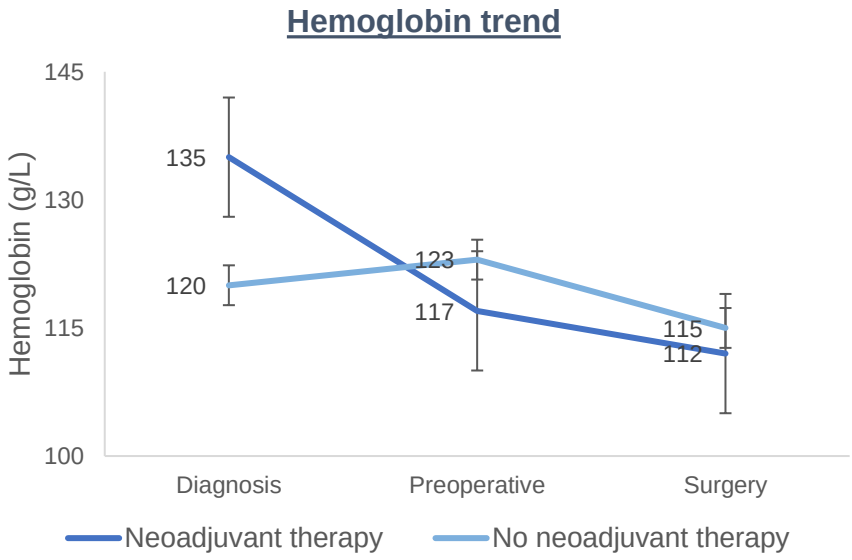

Figure 3. Variation of hemoglobin during diagnosis and treatment

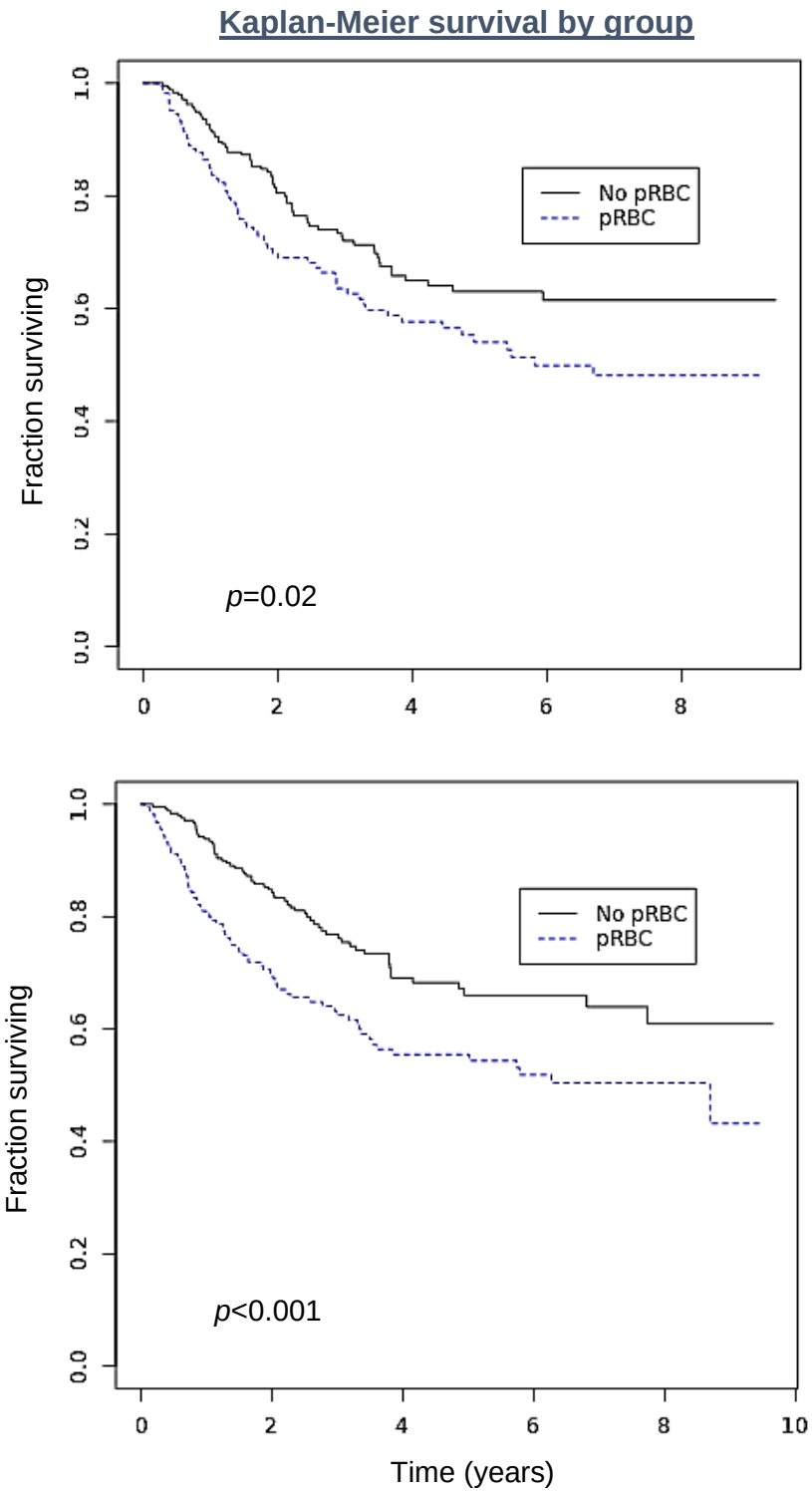

Figure 4. Kaplan-Meier survival curves for disease-free (top) and overall (bottom) survival.

Kaplan-Meier survival by number of pRBC units transfused

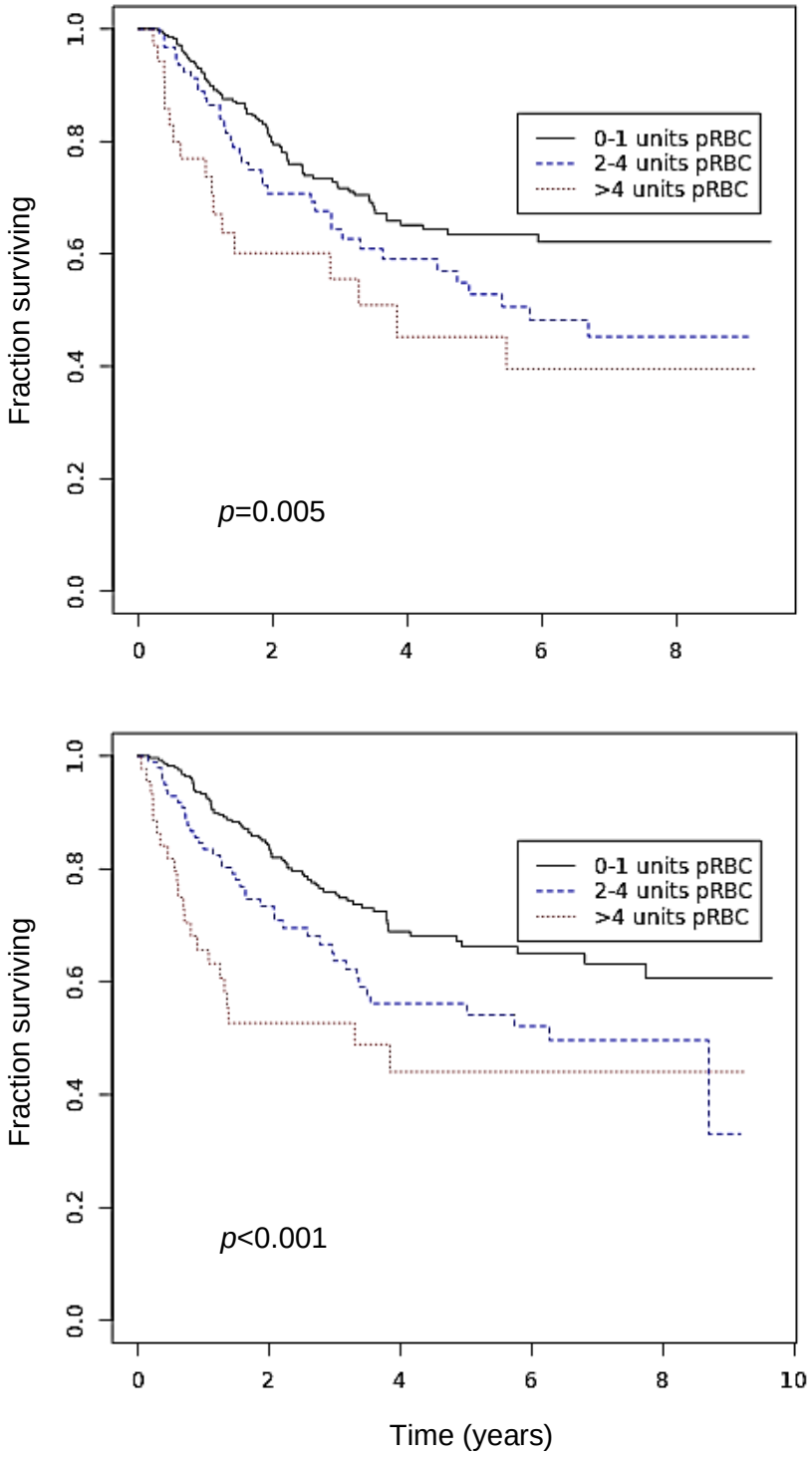

Figure 5. Kaplan-Meier survival curves grouped by quantity of pRBC units transfused for disease-free (top) and overall (bottom) survival.

Table 1. Patient characteristics by group

	Overall (*n* = 435)	**pRBC (*n* = 184)**	**No pRBC (*n* = 251)**	***p* value**
Male sex, *n* (%)	334 (77)	134 (73)	200 (80)	0.119
Age (years), Mdn [IQR]	67 [59-75]	68 [60-76]	65 [59-73]	**0.010**
BMI (kg/m^2), $\bar{x} \pm \sigma_x$	26 ± 5	25 ± 5	26 ± 5	**0.003**
CCI, *n* (%)				**0.008**
1-2 points (mild)	20 (5)	4 (2)	16 (6)	
3-4 points (mod)	193 (44)	72 (39)	121 (48)	
≥5 points (severe)	222 (51)	108 (59)	114 (45)	
Tumour location, *n* (%)				**0.008**
GEJ	270 (62)	111 (60)	159 (63)	
Stomach	125 (29)	47 (26)	78 (31)	
Esophagus	40 (9)	26 (14)	14 (6)	
Histology, *n* (%)				**0.026**
ADC	390 (90)	158 (86)	232 (92)	
SCC	45 (10)	26 (14)	19 (8)	
Grade, *n* (%)				0.354
1	44 (10)	16 (9)	28 (11)	
2	166 (38)	67 (36)	99 (39)	
3	197 (45)	91 (49)	106 (42)	
Her2 positive, *n* (%)	20 (5)	9 (5)	11 (4)	0.786
Clinical stage, *n* (%)				**0.002**

0	3 (1)	0 (0)	3 (1)	
I	57 (13)	17 (9)	40 (16)	
II	78 (18)	23 (13)	55 (22)	
III	207 (48)	100 (54)	107 (43)	
IV	10 (2)	6 (3)	4 (2)	
Tumour extension *n* (%)				**< 0.001**
Tis	3 (1)	0 (0)	3 (1)	
T1	41 (9)	10 (5)	31 (12)	
T2	50 (11)	13 (7)	37 (15)	
T3	272 (63)	124 (67)	148 (59)	
T4	16 (4)	11 (6)	5 (2)	
Node status, *n* (%)				**0.006**
N0	202 (46)	72 (39)	130 (52)	
N+	180 (41)	89 (48)	91 (36)	
Distant metastasis, *n* (%)				0.701
M0	389 (89)	164 (89)	225 (90)	
Mx	11 (3)	4 (2)	7 (3)	
Neoadjuvant therapy, *n* (%)	284 (65)	124 (67)	160 (64)	0.570
nCT	234 (54)	99 (54)	135 (54)	
nCRT	43 (10)	21 (11)	22 (9)	
nCI/O	4 (1)	2 (1)	2 (1)	

Hematology at diagnosis, Mdn [IQR]				
Hb (g/L)	132 [114-145]	124 [108-138]	137 [119-148]	**< 0.001**
HCT (vol%)	0.392 [0.342-0.430]	0.369 [0.330-0.412]	0.410 [0.362-0.440]	**< 0.001**
pRBC during workup, Mdn [IQR]	0 [0-2]	0 [0-2]	0 [0-1]	0.342
Preoperative hematology, Mdn [IQR]				
Hb (g/L)	118 [108-131]	109 [99-120]	126 [115-138]	**< 0.001**
HCT (vol%)	0.360 [0.324-0.391]	0.327 [0.298-0.365]	0.378 [0.345-0.410]	**< 0.001**
PT (s)	12.5 [11.5-13.4]	12.5 [11.5-13.4]	12.5 [11.5-13.3]	0.764
INR	1.01 [0.95-1.06]	1.01 [0.96-1.06]	1.00 [0.95-1.06]	0.271
aPTT (s)	27.3 [24.9-34.5]	26.9 [24.6-33.7]	28.4 [25.1-34.7]	0.222
Hematology on day of surgery, Mdn [IQR]				

Hb (g/L)	113 [99-124]	102 [89-113]	121 [115-132]	**< 0.001**
HCT (vol%)	0.333 [0.290-0.371]	0.302 [0.272-0.334]	0.366 [0.343-0.390]	**< 0.001**
Preop pRBC, Mdn [IQR]	0 [0-0]	0 [0-0]	0 [0-0]	0.631
ERAS pathway, *n* (%)	389 (89)	161 (88)	228 (91)	0.807

† adenosquamous, medullary and neuroendocrine carcinoma

ADC, adenocarcinoma; aPTT, activated partial thromboplastin time; BMI, body mass index; CCI, age-adjusted Charlson comorbidity index; ERAS, enhanced recovery after surgery; GE, gastroesophageal; GEJ, gastroesophageal junction; Hb, hemoglobin; HCT, hematocrit; INR, international normalized ratio; IQR, interquartile range; Mdn, median; nCI/O, neoadjuvant chemoimmunotherapy; nCRT, neoadjuvant chemoradiotherapy; nCT, neoadjuvant chemotherapy; pRBC, packed red blood cell transfusion; PT, prothrombin time; s, seconds; SCC, squamous cell carcinoma; Tis, carcinoma in situ; vol%, volume percentage; $\bar{x}$, mean; σ_X, standard deviation

Table 2. Operative outcomes for each study group

	Overall	**pRBC**	**No pRBC**	***p* value**
Approach, *n* (%)				**<0.001**
Open	315 (72)	151 (82)	164 (65)	
Minimally invasive	112 (26)	28 (15)	84 (33)	
Converted	8 (2)	5 (3)	3 (1)	
Procedure, *n* (%)				0.692

Ivor Lewis esophagectomy	187 (43)	76 (41)	111 (44)	
Subtotal gastrectomy	84 (19)	26 (14)	58 (23)	
LTA esophago-gastrectomy or extended total gastrectomy	55 (13)	25 (14)	30 (12)	
Total gastrectomy	42 (10)	24 (13)	18 (7)	
McKeown esophagectomy	35 (8)	13 (7)	22 (9)	
Transhiatal distal esophagectomy	21 (5)	11 (6)	10 (4)	
Complex esophagectomy†	11 (3)	9 (5)	2 (1)	
Lymphadenectomy, *n* (%)				0.633
D1	32 (7)	16 (9)	16 (6)	
D2	395 (91)	165 (90)	230 (92)	
D3	4 (1)	2 (1)	2 (1)	
Sx duration (min), Mdn [IQR]	210 [172-264]	220 [180-270]	210 [163-259]	0.057
EBL (mL), Mdn [IQR]	300 [200-500]	500 [250-750]	250 [150-400]	**<0.001**
Intra-op pRBC, Mdn [IQR]	0 [0-0]	1 [0-2]	0 [0-0]	**<0.001**
Post-op pRBC, Mdn [IQR]	0 [0-1]	1 [0-2]	0 [0-0]	**<0.001**
Peri-op pRBC, Mdn [IQR]	0 [0-2]	2 [2-4]	0 [0-0]	**<0.001**
LOS (days), Mdn [IQR]	7 [6-12]	10 [7-18]	7 [6-8]	**<0.001**
30-day ER visits, *n* (%)	53 (12)	24 (13)	29 (12)	0.628

30-day readmissions, *n* (%)	45 (10)	16 (9)	29 (12)	0.381
30-day complications, *n* (%)				**<0.001**
CDS 0	134 (31)	22 (12)	112 (45)	
CDS 1-2	191 (44)	92 (50)	99 (39)	
CDS 3-4	93 (21)	56 (30)	37 (15)	
CDS 5	16 (4)	14 (8)	2 (1)	

[†]laryngopharyngoesophagectomy, modified radical neck dissections, interposition flaps

CDS, Clavien–Dindo score; D1, less extensive lymphadenectomy; D2, extended systemic lymphadenectomy; D3, more extended lymphadenectomy; EBL, estimated blood loss; ER, emergency room; IQR, interquartile range; LOS, length of stay; LTA, left thoracoabdominal; Mdn, median; postop, postoperative; pRBC, packed red blood cell transfusion; sx, surgery

Table 3. Complications by group

Name of complication, *n* (%)	Overall	pRBC	No pRBC	*p* value
Atrial arrhythmia	54 (12)	27 (15)	27 (11)	0.234
Anastomotic leak	39 (9)	27 (15)	12 (5)	**<0.001**
Pneumonia	38 (9)	21 (11)	17 (7)	0.098
Urinary retention	37 (9)	12 (7)	25 (10)	0.238
Reintubation	26 (6)	21 (11)	5 (2)	**<0.001**
Pleural effusion	23 (5)	15 (8)	8 (3)	0.024
***C. difficile* colitis**	18 (4)	10 (5)	8 (3)	0.244

Urinary tract infection	15 (3)	9 (5)	6 (2)	0.158
Pulmonary embolus	8 (2)	6 (3)	2 (1)	0.059
Surgical site infection	8 (2)	7 (4)	1 (0)	**0.009**
Conduit necrosis	7 (2)	4 (2)	3 (1)	0.417
Abdominal abscess	6 (1)	3 (2)	3 (1)	0.691
Myocardial infarction	6 (1)	6 (3)	0 (0)	**0.004**
DVT	5 (1)	4 (2)	1 (0.4)	0.085
Pneumothorax	5 (1)	2 (1)	3 (1)	0.928
RLN injury	5 (1)	3 (2)	2 (1)	0.415
Bowel obstruction	4 (1)	2 (1)	2 (1)	0.746
Septic shock	4 (1)	3 (2)	1 (0.4)	0.181
Pericardial effusion	3 (1)	1 (1)	2 (1)	0.761
Cerebrovascular accident	2 (0.5)	2 (1)	0 (0)	0.097
Splenectomy, unplanned	2 (0.5)	2 (1)	0 (0)	0.097

C. difficile, *Clostridioides difficile*; DVT, deep vein thrombosis; RLN, recurrent laryngeal nerve

Table 4. Oncologic outcomes by group

	Overall	**pRBC**	**No pRBC**	***p* value**
Tumour size† (cm), $\bar{x} \pm \sigma_x$	3.7 ± 2.8	4.3 ± 3.2	3.3 ± 2.4	**0.003**
LNs, Mdn [IQR]				
Positive	1 [0-4]	2 [0-7]	1 [0-3]	**0.031**
Total removed	32 [23-44]	33 [24-46]	31 [23-41]	0.114

LVI, *n* (%)				0.775
Yes	221 (51)	97 (53)	124 (49)	
No	178 (41)	72 (39)	106 (42)	
Equivocal	18 (4)	8 (4)	10 (4)	
PNI, *n* (%)				0.648
Yes	212 (49)	94 (51)	118 (47)	
No	190 (44)	76 (41)	114 (45)	
Equivocal	4 (1)	2 (1)	2 (1)	
Location in esophagus, *n* (%)				**<0.001**
Lower third	70 (16)	21 (11)	49 (20)	
Middle third	25 (6)	20 (11)	5 (2)	
Upper third	4 (1)	3 (2)	1 (0.4)	
GEJ classification, *n* (%)				**<0.001**
Siewert I	9 (2)	3 (2)	6 (2)	
Siewert II	118 (27)	40 (22)	78 (31)	
Siewert III	48 (11)	30 (16)	18 (7)	
Gastric location, *n* (%)				0.695
Proximal	221 (51)	95 (52)	126 (50)	
Distal	67 (15)	25 (14)	42 (17)	
Body	45 (10)	18 (10)	27 (11)	
AJCC stage, *n* (%)				0.180
Stage 0	7 (2)	2 (1)	5 (2)	
Stage I	127 (29)	46 (25)	81 (32)	

Stage II	77 (18)	31 (17)	46 (18)	
Stage III	185 (43)	83 (45)	102 (41)	
Stage IV	39 (9)	22 (12)	17 (7)	
Tumour extension, *n* (%)				**<0.001**
T0	24 (6)	9 (5)	15 (6)	
Tis	4 (1)	1 (0.5)	3 (1)	
T1	93 (21)	27 (15)	66 (26)	
T2	67 (15)	23 (13)	44 (18)	
T3	195 (45)	90 (49)	105 (42)	
T4	52 (12)	34 (18)	18 (7)	
Node status, *n* (%)				**<0.001**
N0	182 (42)	78 (42)	104 (41)	
N1	91 (21)	25 (14)	66 (26)	
N2	87 (20)	36 (20)	51 (20)	
N3	75 (17)	45 (24)	30 (12)	
M0, *n* (%)	435 (100)	184 (100)	251 (100)	0.900
pCR, *n* (%)	20 (7)	8 (6)	12 (8)	0.856
Positive margin, *n* (%)	5 (1)	1 (1)	4 (2)	0.319

[†]greatest dimension of tumour as measured by pathologist

AJCC, American Joint Committee on Cancer; cm, centimeters; GEJ, gastroesophageal junction; IQR, interquartile range; LN, lymph node; LVI, lymphovascular invasion; M, distant metastasis; Mdn, median; N, lymph node metastasis; pCR, pathologic complete

response; PNI, perineural invasion; pRBC, packed red blood cell transfusion; T, tumour extension; $\bar{x}$, mean; σ_X, standard deviation

Table 5. Quality of life scores† from FACT-E questionnaires for each group

	Overall	**pRBC**	**No pRBC**	***p* value**
Pre-neoadjuvant therapy	114 [95-135]	109 [96-132]	118 [96-136]	0.497
Preoperative visit	122 [103-138]	120 [102-135]	123 [106-140]	0.254
First postop visit	112 [97-128]	111 [99-126]	115 [95-131]	0.549
3 months postop	125 [110-141]	131 [114-141]	114 [106-140]	0.254
6 months postop	131 [102-141]	129 [109-139]	132 [101-149]	0.682
12 months postop	128 [113-152]	128 [116-148]	130 [108-153]	0.818
18 months postop	141 [128-153]	142 [134-152]	140 [120-154]	0.749
2 years postop	138 [126-152]	138 [132-157]	150 [118-149]	0.312
3 years postop	140 [124-159]	145 [119-164]	140 [127-153]	0.912

†reported as median [interquartile range]

FACT-E, Functional Assessment of Cancer Therapy-Esophageal; postop, postoperative

Table 6. Cox proportional hazard analysis for disease-free survival

	HR	**95% Confidence Interval**	***p* value**
pRBC 0-2 units	1.002	[0.643 – 1.562]	0.993
pRBC 3-4 units	1.382	[0.710 – 2.687]	0.341
pRBC >4 units	1.239	[0.685 – 2.243]	0.479
Neoadjuvant therapy	0.606	[0.384 – 0.956]	**0.031**

Major complications	288	[24 – 3436]	**<0.001**
Pathological tumour stage (T4)†	4.454	[1.332 – 14.894]	**0.015**
Pathological nodal stage†			
N1	3.347	[1.839 – 6.092]	**<0.001**
N2	3.435	[1.845 – 6.395]	**<0.001**
N3	4.182	[2.217 – 7.889]	**<0.001**
Age 60+ years	1.062	[0.562 – 2.008]	0.853
Comorbidities (severe)	0.826	[0.348 – 1.962]	0.666
Female sex	1.096	[0.715 – 1.680]	0.675
Open approach vs. MIS	1.141	[0.682 – 1.908]	0.615
Gastrectomy vs. esophagectomy	0.640	[0.402 – 1.019]	0.060
Tumour size >3 cm	1.029	[0.690 – 1.534]	0.889

†stage 0 used as reference

HR, hazard ratio; MIS, minimally invasive surgery; N, extend of lymph node metastasis; pRBC, packed red blood cells; T, tumour extension; vs., versus

Table 7. Cox proportional hazard analysis for overall survival

	HR	**95% Confidence Interval**	***p* value**
Transfusion	0.956	[0.644 – 1.420]	0.825
Major complications	228	[86 – 606]	**<0.001**
Pathological tumour stage (T4)†	4.570	[1.312 – 15.912]	**0.017**
Pathological nodal stage†			
N1	1.226	[0.718 – 2.094]	0.456

N2	1.746	[1.017 – 2.998]	**0.044**
N3	1.832	[1.042 – 3.221]	**0.035**
Gastrectomy vs. esophagectomy	0.561	[0.366 – 0.861]	**0.008**
Tumour size > 3 cm	1.454	[0.983 – 2.151]	**0.061**

[†]stage 0 used as reference

CDS, Clavien-Dindo score; HR, hazard ratio; vs., versus

Table 8. Multivariate analysis for prognostic factors of perioperative red cell transfusion

Risk factor	**OR**	**95% Confidence Interval**	***p* value**
Age >60 years	1.105	[0.408 – 2.989]	0.845
Anemia (moderate-severe)	6.208	[3.342 – 11.530]	**<0.001**
Blood loss > 400 mL	4.878	[2.657 – 8.954]	**<0.001**
Female sex	2.827	[1.425 – 5.608]	**0.003**
Gastrectomy vs. esophagectomy	1.445	[0.673 – 3.100]	0.345
Neoadjuvant therapy	0.749	[0.326 – 1.720]	0.496
Open approach vs. MIS	4.048	[1.724 – 9.504]	**0.001**
Operative time (minutes)	1.008	[1.002 – 1.014]	**0.005**
Locally advanced cancer	1.594	[0.598 – 4.244]	0.351
Comorbidities (severe)	9.954	[0.829 – 119]	0.070
Body mass index	1.225	[0.321 – 4.684]	0.766

MIS, minimally invasive surgery; mL, millilitres; mod, moderate; OR, odds ratio; vs., versus

APPENDIX

Appendix I: List of Abbreviations

ADC	adenocarcinoma
AJCC	American Joint Committee on Cancer
aPTT	activated partial thromboplastin time
BE	Barrett's esophagus
BMI	body mass index
C. difficile	*Clostridioides difficile*
CCI	age-adjusted Charlson comorbidity index
CD	cluster of differentiation
CDS	Clavien–Dindo score
cm	centimeters
CT	computed tomography
D1	less extensive lymphadenectomy
D2	extended systemic lymphadenectomy
D3	more extended lymphadenectomy
DFS	disease-free survival
DVT	deep vein thrombosis
EBL	estimated blood loss
ER	emergency room
ERAS	enhanced recovery after surgery
FACT-E	Functional Assessment of Cancer Therapy-Esophageal
FDG-PET	^{18}F-fluorodeoxyglucose positron emission tomography

GEJ	gastroesophageal junction
GERD	gastroesophageal reflux disease
Gy	Gray
H. pylori	*Helicobacter pylori*
Hb	hemoglobin
HCT	hematocrit
HR	hazard ratio
IL	interleukin
INR	international normalized ratio
IQR	interquartile range
LN	lymph node
LOS	length of stay
LPCs	lysophosphatidylcholines
LTA	left thoracoabdominal
LVI	lymphovascular invasion
M	distant metastasis
Mdn	median
MIS	minimally invasive surgery
mL	millilitres
N	extent of lymph node metastasis
nCI/O	neoadjuvant chemoimmunotherapy
nCRT	neoadjuvant chemoradiotherapy
nCT	neoadjuvant chemotherapy

OR	odds ratio
OS	overall survival
pCR	pathologic complete response
PNI	perineural invasion
Postop	postoperative
pRBC	packed red blood cells
Pre-op	preoperative
PT	prothrombin time
QoL	quality of life
R_0	complete oncologic resection (microscopic negative margin)
R_1	microscopic positive margins
R_2	macroscopic positive margin
RLN	recurrent laryngeal nerve
s	seconds
SCC	squamous cell carcinoma
Sx	surgery
T	tumour extension
Tis	carcinoma in situ
TNF-α	tumour necrosis factor alpha
Treg	regulatory T-cell
TRIM	transfusion-related immunomodulation
vol%	volume percentage
WHO	World Health Organization

$\bar{x}$	mean
σ_X	standard deviation

Appendix II: FACT-E questionnaire

Below is a list of statements that other people with your illness have said are important**.**

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	<u>PHYSICAL WELL-BEING</u>	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4

GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
G	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4

GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following*					
GG	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	<u>EMOTIONAL WELL-BEING</u>	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4

GE5	I worry about dying	0	1	2	3	4
GG	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4

GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
G	I am content with the quality of my life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	<u>ADDITIONAL CONCERNS</u>	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**

HN1	I am able to eat the foods that I like	0	1	2	3	4
HN2	My mouth is dry	0	1	2	3	4
HN3	I have trouble breathing	0	1	2	3	4
HN4	My voice has its usual quality and strength	0	1	2	3	4
HN5	I am able to eat as much food as I want	0	1	2	3	4

HN10	I am able to communicate with others	0	1	2	3	4
HN7	I can swallow naturally and easily	0	1	2	3	4
E1	I have difficulty swallowing solid foods	0	1	2	3	4
E2	I have difficulty swallowing soft or mashed foods	0	1	2	3	4
E3	I have difficulty swallowing liquids	0	1	2	3	4
E4	I have pain in my chest when I swallow	0	1	2	3	4

E5	I choke when I swallow	0	1	2	3	4
E6	I am able to enjoy meals with family or friends	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
E7	I wake at night because of coughing	0	1	2	3	4
ACT11	I have pain in my stomach area	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4

Appendix III: FACT-E Scoring Guidelines (Version 4) – Page 1

Instructions:* 1. Record answers in "item response" column. If missing, mark with an X

2. Perform reversals as indicated, and sum individual items to obtain a score.

3. Multiply the sum of the item scores by the number of items in the subscale, then divide by the number of items answered. This produces the subscale score.

4. Add subscale scores to derive total scores (FACT-E).

5. **The higher the score, the better the QOL.**

Subscale	Item Code	Reverse item?		Item response	Item Score
PHYSICAL	GP1	4	-	_____	=_____
WELL-BEING	GP2	4	-	_____	=_____
(PWB)	GP3	4	-	_____	=_____
	GP4	4	-	_____	=_____
Score range: 0-28	GP5	4	-	_____	=_____
	GP6	4	-	_____	=_____
	GP7	4	-	_____	=_____

Sum individual item scores: _____

Multiply by 7: _____

Divide by number of items answered: _____=**PWB subscale score**

SOCIAL/FAMILY	GS1	0	+	_____	=_____
WELL-BEING	GS2	0	+	_____	=_____
(SWB)	GS3	0	+	_____	=_____
	GS4	0	+	_____	=_____
Score range: 0-28	GS5	0	+	_____	=_____
	GS6	0	+	_____	=_____
	GS7	0	+	_____	=_____

Sum individual item scores: _____

Multiply by 7: _____

Divide by number of items answered: _____=**SWB subscale score**

EMOTIONAL	GE1	4	-	_____	=_____
WELL-BEING	GE2	0	+	_____	=_____
(EWB)	GE3	4	-	_____	=_____

Score range: 0-24	GE4	4	-	_____	=_____
	GE5	4	-	_____	=_____
	GE6	4	-	_____	=_____

Sum individual item scores: _____

Multiply by 6: _____

Divide by number of items answered: _____**=<u>EWB subscale score</u>**

FUNCTIONAL	GF1	0	+	_____	=_____
WELL-BEING	GF2	0	+	_____	=_____
(FWB)	GF3	0	+	_____	=_____
	GF4	0	+	_____	=_____
Score range: 0-28	GF5	0	+	_____	=_____
	GF6	0	+	_____	=_____
	GF7	0	+	_____	=_____

Sum individual item scores: _____

Multiply by 7: _____

Divide by number of items answered: _____=**FWB subscale score**

FACT-E Scoring Guidelines (Version 4) – Page 2

Subscale	**Item Code**	**Reverse item?**		**Item response**	**Item Score**
ESOPHAGUS	HN1	0	+	_____	=_____
CANCER	HN2	4	-	_____	=_____
SUBSCALE	HN3	4	-	_____	=_____
(ECS)	HN4	0	+	_____	=_____
	HN5	0	+	_____	=_____
Score range: 0-68	HN10	0	+	_____	=_____
	HN7	0	+	_____	=_____
	E1	4	-	_____	=_____
	E2	4	-	_____	=_____
	E3	4	-	_____	=_____
	E4	4	-	_____	=_____
	E5	4	-	_____	=_____
	E6	0	+	_____	=_____
	C6	0	+	_____	=_____

E7	4	-	_____	=_____
ACT11	4	-	_____	=_____
C2	4	-	_____	=_____

Sum individual item scores: _____

Multiply by 17 : _____

Divide by number of items answered: _____**=EC Subscale score**

To Derive a FACT-E total score:
Score range: 0-176

_____ + _____ + _____ + _____ + _____ =_____=**FACT-E Total score**

(**PWB** score) (**SWB** score) (**EWB** score) (**FWB** score) (**ECS** score)

*For guidelines on handling missing data and scoring options, please refer to the Administration and Scoring Guidelines in the manual or on-line at www.facit.org.