

World Journal of *Gastrointestinal Oncology*

World J Gastrointest Oncol 2020 June 15; 12(6): 604-704





REVIEW

- 604 Real-world evidence on adjuvant chemotherapy in older adults with stage II/III colon cancer
Batra A, Rigo R, Sheka D, Cheung WY

MINIREVIEWS

- 619 Structure and function of Septin 9 and its role in human malignant tumors
Sun J, Zheng MY, Li YW, Zhang SW

ORIGINAL ARTICLE

Retrospective Cohort Study

- 632 Low ligation has a lower anastomotic leakage rate after rectal cancer surgery
Chen JN, Liu Z, Wang ZJ, Zhao FQ, Wei FZ, Mei SW, Shen HY, Li J, Pei W, Wang Z, Yu J, Liu Q

Retrospective Study

- 642 Clinical diagnosis and management of pancreatic mucinous cystadenoma and cystadenocarcinoma: Single-center experience with 82 patients
Zhao ZM, Jiang N, Gao YX, Yin ZZ, Zhao GD, Tan XL, Xu Y, Liu R

Clinical Trials Study

- 651 Fibrin sealant for esophageal anastomosis: A phase II study
Lin YB, Fu JH, Huang Y, Hu YH, Luo KJ, Wang KX, Bella AÉ, Situ DR, Chen JY, Lin T, D'Journo XB, Novoa NM, Brunelli A, Fernando HC, Cerfolio RJ, Ismail M, Yang H, the AME Thoracic Surgery Collaborative Group

Observational Study

- 663 Sorafenib combined with embolization plus hepatic arterial infusion chemotherapy for inoperable hepatocellular carcinoma
Liu BJ, Gao S, Zhu X, Guo JH, Zhang X, Chen H, Wang XD, Yang RJ
- 677 Clinical significance of expression of fibrous sheath interacting protein 1 in colon cancer
Wu HY, Yang B, Geng DH

META-ANALYSIS

- 687 Timing of surgery after neoadjuvant chemoradiotherapy affects oncologic outcomes in patients with esophageal cancer
Shang QX, Yang YS, Gu YM, Zeng XX, Zhang HL, Hu WP, Wang WP, Chen LQ, Yuan Y

CASE REPORT

- 699** Immune checkpoint inhibitors induced colitis, stay vigilant: A case report
Abu Khalaf S, Albarrak A, Yousef M, Tahan V

ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Oncology*, Nuri Faruk Aykan, MD, Professor, Department of Medical Oncology, Istinye University, Bahcesehir Liv Hospital, Istanbul 34510, Turkey

AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Oncology* (WJGO, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including islet cell adenoma, liver cell adenoma, adenomatous polyposis coli, appendiceal neoplasms, bile duct neoplasms, biliary tract neoplasms, hepatocellular carcinoma, islet cell carcinoma, pancreatic ductal carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, hereditary nonpolyposis colorectal neoplasms, common bile duct neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, etc.

INDEXING/ABSTRACTING

The WJGO is now indexed in Science Citation Index Expanded (also known as SciSearch®), PubMed, and PubMed Central. The 2019 edition of Journal Citation Reports® cites the 2018 impact factor for WJGO as 2.758 (5-year impact factor: 3.220), ranking WJGO as 52 among 84 journals in gastroenterology and hepatology (quartile in category Q3), and 131 among 229 journals in oncology (quartile in category Q3).

RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: *Lu-Lu Qi*

Proofing Production Department Director: *Xiang Li*

Responsible Editorial Office Director: *Jin-Lai Wang*

NAME OF JOURNAL

World Journal of Gastrointestinal Oncology

ISSN

ISSN 1948-5204 (online)

LAUNCH DATE

February 15, 2009

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Monjur Ahmed, Rosa M Jimenez Rodriguez, Pashtoon Kasi

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/1948-5204/editorialboard.htm>

PUBLICATION DATE

June 15, 2020

COPYRIGHT

© 2020 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Clinical Trials Study

Fibrin sealant for esophageal anastomosis: A phase II study

Yao-Bin Lin, Jian-Hua Fu, Yan Huang, Yi-Huai Hu, Kong-Jia Luo, Ke-Xi Wang, Amos Éla Bella, Dong-Rong Situ, Ji-Yang Chen, Ting Lin, Xavier B D'Journo, Nuria M Novoa, Alessandro Brunelli, Hiran C Fernando, Robert J Cerfolio, Mahmoud Ismail, Hong Yang, the AME Thoracic Surgery Collaborative Group

ORCID number: Yao-Bin Lin (0000-0002-0601-2024); Jian-Hua Fu (0000-0001-6304-5562); Yan Huang (0000-0002-9791-5527); Yi-Huai Hu (0000-0003-0916-3407); Kong-Jia Luo (0000-0002-0814-061X); Ke-Xi Wang (0000-0001-6038-8404); Amos Éla Bella (0000-0002-7313-6465); Dong-Rong Situ (0000-0002-0832-1023); Ji-Yang Chen (0000-0002-7488-4393); Ting Lin (0000-0002-4226-7649); Xavier B D'Journo (0000-0001-6747-4583); Nuria M Novoa (0000-0003-0124-6347); Alessandro Brunelli (0000-0002-6505-1656); Hiran C Fernando (0000-0002-5330-7036); Robert J Cerfolio (0000-0002-5598-599X); Mahmoud Ismail (0000-0003-4501-0950); Hong Yang (0000-0002-6007-9086).

Author contributions: Yang H and Fu JH contributed equally to the supervision of the study and share co-senior authorship; Yang H, Fu JH, and Lin YB conceived of the study and contributed to project design; Yang H, Fu JH, Lin YB, Huang Y, Hu YH, Luo KJ, and Wang KX recruited patients for the study; Lin YB, Huang Y, Hu YH, Chen JY, and Ling T performed data collection; Yang H, Lin YB, Huang Y, Hu YH, Éla Bella A, and Situ DR analyzed and interpreted the data; Lin YB, Huang Y, Hu YH, Luo KJ, Éla Bella A, and Situ DR drafted the manuscript; Yang H, Fu JH, D'Journo XB, Novoa NM, Brunelli A, Fernando HC, Cerfolio RJ, and Ismail M contributed to editing and revising the article; all

Yao-Bin Lin, Jian-Hua Fu, Yan Huang, Yi-Huai Hu, Kong-Jia Luo, Ke-Xi Wang, Ji-Yang Chen, Ting Lin, Hong Yang, Department of Thoracic Surgery, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangdong Esophageal Cancer Institute, Sun Yat-sen University Cancer Center, Guangzhou 510060, Guangdong Province, China

Amos Éla Bella, Department of Thoracic Surgery, Avicenne Hospital, Bobigny 93000, France

Amos Éla Bella, Department of Surgery and Specialties, Faculty of Medicine and Biomedical Sciences, University of Yaoundé I, Yaoundé, Cameroon

Dong-Rong Situ, Department of Surgery, Royal Darwin Hospital, Northern Territory 0811, Australia

Xavier B D'Journo, Department of Thoracic Surgery and Diseases of Esophagus, Aix-Marseille University, Hôpital Nord, Marseille 13915, France

Nuria M Novoa, Thoracic Surgery Service, University Hospital of Salamanca, Salamanca 37007, Spain

Alessandro Brunelli, Department of Thoracic Surgery, St James's University Hospital, Leeds LS9 7TF, United Kingdom

Hiran C Fernando, Section of Thoracic Surgery, Inova Fairfax Medical Center, Inova Schar Cancer Institute, Falls Church, VA 22042, United States

Robert J Cerfolio, Department of Cardiothoracic Surgery, New York University Langone Health, New York, NY 10016, United States

Mahmoud Ismail, Department of Thoracic Surgery, Academic Hospital of the Charité–Universitätsmedizin, Humboldt University Berlin, Berlin 10117, Germany

Corresponding author: Hong Yang, MD, PhD, Associate Professor, Chief, Department of Thoracic Surgery, Sun Yat-sen University Cancer Center, 651 Dongfeng Road East, Guangzhou 510060, Guangdong Province, China. yanghong@sysucc.org.cn

Abstract

BACKGROUND

Esophagectomy is a pivotal curative modality for localized esophageal or esophagogastric junction cancer (EC or EJC). Postoperative anastomotic leakage

authors read and approved the final version.

Supported by Fundamental Research Funds for the Central Universities, No. 17ykzd30; National Natural Science Foundation of China, No. 81972614; Guangdong Esophageal Cancer Institute Science and Technology Program, No. M201601; Health & Medical Collaborative Innovation Project of Guangzhou City, China, No. 201803040018.

Institutional review board

statement: The study was reviewed and approved by the Ethics Committee of Sun Yat-sen University Cancer Center.

Clinical trial registration statement:

This study is registered at <https://clinicaltrials.gov> (No. NCT03529266).

Informed consent statement: All study participants provided written informed consent prior to study enrolment.

Conflict-of-interest statement: All authors have completed the Unified Competing Interest form and declare the following potential conflicts of interest: Robert J Cerfolio received non-financial support from Intuitive, Inc., Ethicon, Inc., Covidien, Inc., Bovie, Inc., KCL, Inc., Myriad, Inc., Neomend/BARD, Inc., Novartis, Inc., Pinnacle, Inc., TransEnteric, Inc., Medtronic, Inc., Google, Inc., C-SATS video review, Inc., ConMed/AirSeal, Inc., and Aztraseneca, Inc. Robert J Cerfolio is president of ROLO -7 Consulting Firm. The remaining authors declare no conflict of interest.

Data sharing statement: The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

CONSORT 2010 statement: The manuscript was updated according to the CONSORT 2010.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and

(AL) remains problematic. The use of fibrin sealant (FS) may improve the strength of esophageal anastomosis and reduce the incidence of AL.

AIM

To assess the efficacy and safety of applying FS to prevent AL in patients with EC or EJC.

METHODS

In this single-arm, phase II trial (Clinicaltrial.gov identifier: NCT03529266), we recruited patients aged 18-80 years with resectable EC or EJC clinically staged as T1-4aN0-3M0. An open or minimally invasive McKeown esophagectomy was performed with a circular stapled anastomosis. After performing the anastomosis, 2.5 mL of porcine FS was applied circumferentially. The primary endpoint was the proportion of patients with AL within 3 mo.

RESULTS

From June 4, 2018, to December 29, 2018, 57 patients were enrolled. At the data cutoff date (June 30, 2019), three (5.3%) of the 57 patients had developed AL, including two (3.5%) with esophagogastric AL and one (1.8%) with gastric fistula. The incidence of anastomotic stricture and other major postoperative complications was 1.8% and 17.5%, respectively. The median time needed to resume oral feeding after operation was 8 d (Interquartile range: 7.0-9.0 d). No adverse events related to FS were recorded. No deaths occurred within 90 d after surgery.

CONCLUSION

Perioperative sealing with porcine FS appears safe and may prevent AL after esophagectomy in patients with resectable EC or EJC. Further phase III studies are warranted.

Key words: Esophageal cancer; McKeown esophagectomy; Fibrin sealant; Anastomotic leakage; Postoperative complications; Prevention

©The Author(s) 2020. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: The application of fibrin sealant (FS) in esophageal surgery is an attractive therapeutic strategy to prevent anastomotic leakage. In this study, the efficacy and safety of FS were assessed in 57 patients with resectable esophageal or junctional cancer undergoing McKeown esophagectomy. Our findings showed that perioperative sealing with FS was safe and effective for preventing AL in patients with esophageal or junctional cancer, supporting further investigation in phase III trials and implementation in clinical practice.

Citation: Lin YB, Fu JH, Huang Y, Hu YH, Luo KJ, Wang KX, Bella AE, Situ DR, Chen JY, Lin T, D'Journo XB, Novoa NM, Brunelli A, Fernando HC, Cerfolio RJ, Ismail M, Yang H, the AME Thoracic Surgery Collaborative Group. Fibrin sealant for esophageal anastomosis: A phase II study. *World J Gastrointest Oncol* 2020; 12(6): 651-662

URL: <https://www.wjnet.com/1948-5204/full/v12/i6/651.htm>

DOI: <https://dx.doi.org/10.4251/wjgo.v12.i6.651>

INTRODUCTION

Esophageal cancer (EC) is the seventh most common malignancy worldwide^[1]. In China, approximately 477900 new diagnoses and 375000 deaths in 2015 were estimated to be due to EC, accounting for more than half of the global morbidity and mortality^[1,2]. Currently, surgery remains a routine component of treatment for esophageal or esophagogastric junction cancer (EJC). McKeown esophagectomy, consisting of a cervical anastomosis, is one of the most commonly used procedures, as it provides the potential advantages of adequate resection and extensive lymphadenectomy^[3]. However, compared with intrathoracic anastomosis after esophagectomy, the cervical anastomosis is associated with a higher risk of

the use is non-commercial. See:
<http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Unsolicited manuscript

Received: January 20, 2020

Peer-review started: January 20, 2020

First decision: March 24, 2020

Revised: March 28, 2020

Accepted: May 5, 2020

Article in press: May 5, 2020

Published online: June 15, 2020

P-Reviewer: Krishnan A, Steenholdt C, Vermeire S

S-Editor: Wang JL

L-Editor: Wang TQ

E-Editor: Qi LL



postoperative complications, especially anastomotic leakage (AL)^[4,5].

AL is one of the most severe postoperative complications and results in a prolonged hospital stay, increased cost, and considerable morbidity and mortality^[5,6]. The incidence of esophageal AL remains high at a range of 10.6%-26.1% worldwide^[7-10]. A variety of anastomotic methods have been developed to prevent AL after esophagectomy, including the application of fibrin sealant (FS) to the anastomosis. FS could strengthen the anastomosis and promote anastomotic healing by enabling polymerization and forming tight approximation of the anastomosis^[11,12]. However, the results from clinical trials exploring the use of FS as an anastomotic sealant in esophageal surgery have been inconsistent^[13-17]. To date, only two pilot studies have been conducted to investigate the use of FS in routine esophagectomy for EC^[15,16]. The current phase II trial enrolled patients undergoing McKeown surgery for EC or EJC, and aimed to evaluate the efficacy and safety of applying porcine FS to prevent AL.

MATERIALS AND METHODS

Study design

This study was a single-center, single-arm, open-label, phase II clinical trial conducted at Sun Yat-sen University Cancer Center in Guangzhou, China. The study obtained approval from the ethics committee of Sun Yat-sen University Cancer Center and was conducted according to the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines. All included patients provided written informed consent.

This trial is registered at ClinicalTrials.gov, number NCT03529266.

Participants

Eligible patients were aged from 18 to 80 years with histologically proven squamous cell carcinoma or adenocarcinoma of the thoracic esophagus or esophagogastric junction staged as T1-4aN0-3M0 (according to the International Union Against Cancer and American Joint Committee on Cancer Staging System for Esophagus and Esophagogastric Junction, eighth edition). An Eastern Cooperative Oncology Group performance status of 0 to 1, normal bone marrow function, and adequate hepatic and renal function were also required. The exclusion criteria included salvage esophagectomy after failed definitive chemoradiotherapy; a history of diabetes spanning more than a decade and uncontrolled blood glucose level; allergy to any ingredients of FS.

Treatment and procedures

All patients underwent the following workup for diagnosis and pretreatment staging: Contrast esophagography; plain and enhanced computed tomography (CT) of the chest and abdomen; cervical ultrasonography; esophagogastroduodenoscopy (EGD) with endoscopic ultrasound; electronic bronchoscopy or endobronchial ultrasound to confirm involvement of the trachea and/or bronchus, if indicated; positron emission tomography-CT to rule out distant metastasis, if indicated.

An open or minimally invasive radical resection of the primary tumor was performed by one surgical team led by one of the authors (Yang H) using the McKeown esophagectomy, combined with a two-field lymphadenectomy. The dissected lymph nodes included bilateral recurrent laryngeal nerve nodes, left lower paratracheal nodes, upper/middle/lower thoracic paraesophageal nodes, subcarinal nodes, posterior mediastinal nodes, paracardiac nodes, lesser curvature nodes, left gastric nodes, common hepatic nodes, splenic nodes, and celiac nodes. After esophageal resection, anastomosis was performed in an end-to-side fashion between the esophagus and tubularized stomach or colon *via* a neck incision using a circular stapler (EEA 21 or 25, Covidien, USA), with the staple line inverted by a whole-layer suture (3-0 Vicryl, Ethicon, USA). The blind end of the gastric conduit or colon was closed using a 60-mm linear stapler (Endo GIA, Covidien, USA; or Echelon Flex, Ethicon, USA) and oversewn with a seromuscular-layer suture (3-0 Vicryl, Ethicon, USA).

After complete irrigation of the surgical field, 2.5 ml of FS [Bioseal®, Guangzhou Bioseal Biotech—Subsidiary of Johnson & Johnson (China) Investment Ltd, China] was applied to the anastomosis circumferentially. A nasogastric tube, a subcutaneous drainage tube in the neck, and two chest tubes, as well as a feeding tube in the jejunum by jejunostomy, were placed intraoperatively. Details of the anastomotic technique with intraoperative application of FS to the cervical anastomosis are shown in [Figure 1](#).

After surgery, all patients were treated in the intensive care unit on the day of

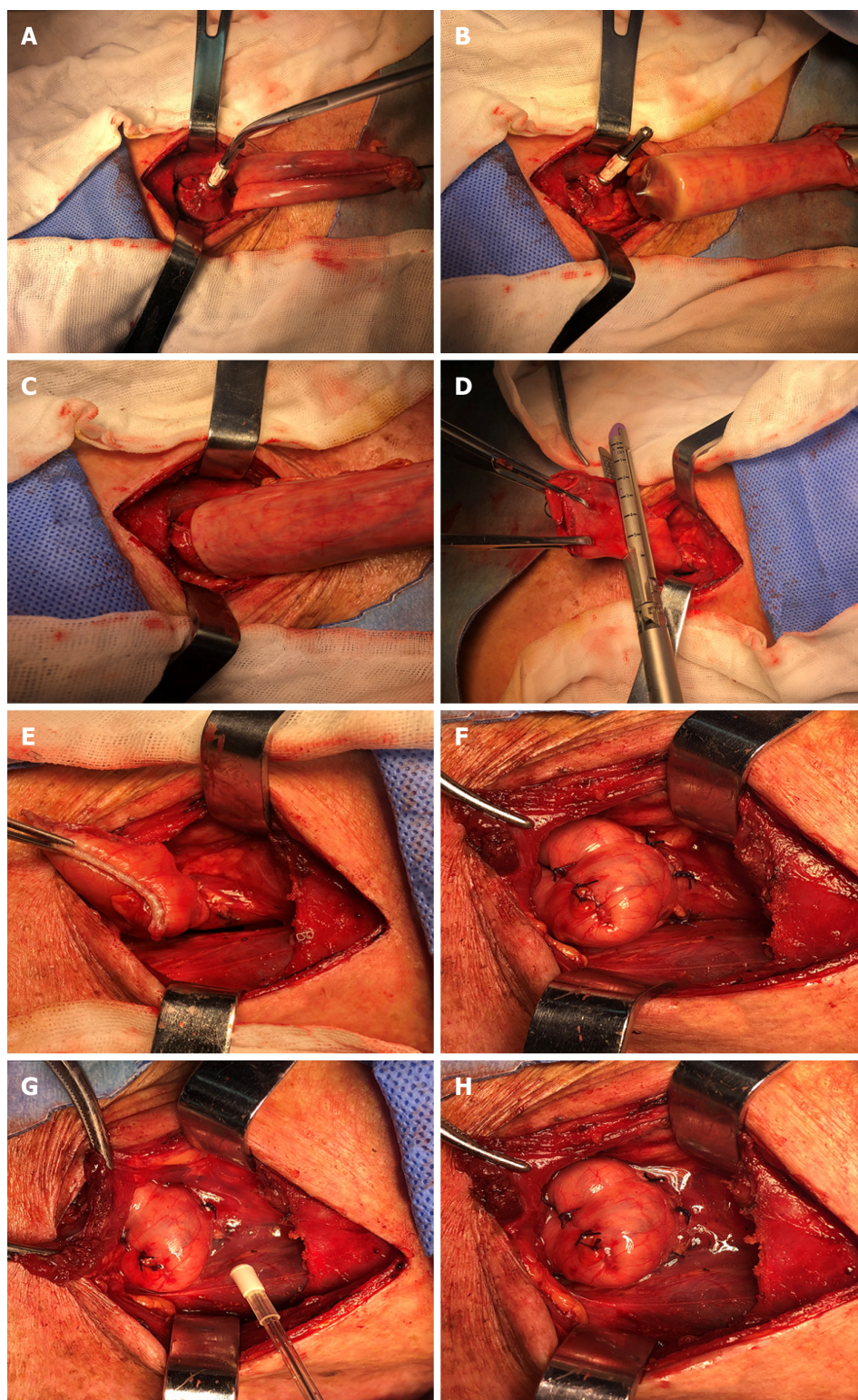


Figure 1 Illustration of the circular stapled anastomosis with application of fibrin sealant to esophagogastric anastomosis after esophageal resection. A: The stapler head was placed into cervical esophagus stump and tied carefully; B: Incision of the gastric wall and insert of the stapler; C: Esophagogastric end-to-side anastomosis with a circular stapler; D: Closure of the fundus of gastric conduit with a linear stapler; E: Anastomosis and gastric stump after circular stapling; F: The staple line was inverted with a whole-layer suture; G: Fibrin sealant was applied to the esophagogastric anastomosis circumferentially; H: Completion of the application of fibrin sealant to cervical anastomosis.

operation and re-admitted to the general ward the next day for routine postoperative rehabilitation. The nasogastric tube was removed one day later if there was no occurrence of anastomotic hemorrhage. Evaluations of AL were routinely performed by contrast esophagography 7 d postoperatively, unless the examination was clinically contraindicated, such as for patients who were intubated due to respiratory failure. Adequate nutrition through enteral or parenteral nutritional support was

ensured before oral intake. Modified oral feeding with recommended diet was allowed after confirming the absence of AL.

Outcome measurement

The primary endpoint was the proportion of patients with AL within the first 3 mo after operation. Patients with saliva, gastrointestinal content, or drainage stained by oral methylene blue dye collected from the neck or chest tubes were suspected to have AL, and then EGD or contrast esophagography was performed for further confirmation^[18]. Diagnosis of AL was mainly established by the independent image committee depending on the visualization of total parietal defects involving the esophagus, anastomosis, staple line, or gastric tube during EGD carried out by an experienced endoscopist, or extravasation of barium during contrast esophagography^[19].

The secondary endpoints were time to first oral feeding, postoperative morbidity rate, especially the postoperative anastomotic stricture rate, and postoperative mortality rate. We defined grades I and II complications as minor complications, and grades III and IV as major complications, according to the Clavien-Dindo classification of surgical complications^[20].

Follow-up

Routine follow-up included outpatient clinic visits once every 3 mo in the first year and then every 6 mo thereafter until the end of the study or death. The follow-up assessments performed at every visit were as follows: Physical examinations; laboratory tests including hematology, chemistry, and tumor markers; chest radiography; contrast swallow study; and ultrasound scans of the neck and abdomen. Patients were also required to undergo enhanced neck/chest/abdomen CT scans and EGD once every year.

Statistical analysis

The study was designed based on Simon's optimal two-stage method with a one-sided α of 0.05 and power of 80%. An anastomotic leakage rate of 5% or less was expected as evidence for the efficacy of FS application (alternative hypothesis), whereas a rate of 15% or more indicated by previous studies^[9,10] was considered insufficient for the assessment to continue (null hypothesis). According to these assumptions, 39 evaluable patients had to be enrolled in the first stage, of whom at least 35 were required to be free from AL. An additional 18 patients would be included in the second stage, leading to a total of 57 patients for the final analyses. Overall, the advantage of FS would be sufficiently proven if 52 or more patients were protected from AL.

We performed analyses based on the intention-to-treat population composed of all enrolled patients. Frequency and percentage were presented for the description of postoperative AL, along with other categorical variables. Medians and interquartile ranges (IQRs), or mean and SD were calculated for the description of continuous variables. Time-to-event data were summarized by Kaplan-Meier methods. We did statistical analyses using SPSS 22.0 (IBM Corporation, USA).

RESULTS

Patient characteristics

Between June 4, 2018, and December 29, 2018, 64 patients were screened, of whom 57 were enrolled in the study and underwent McKeown esophagectomy with an intraoperative application of FS at the Sun Yat-sen University Cancer Center (Figure 2). The median duration of follow-up at the time of data analysis (data cutoff on June 30, 2019) was 10.2 mo (IQR: 8.3-11.5 mo).

Baseline characteristics are summarized in Table 1. The median age was 61 years (range 41-75). Forty-nine (86.0%) of the 57 patients were men. Most tumors were located in the thoracic esophagus [in 47 (82.5%) of 57 patients], while five (8.8%) patients were diagnosed with EJC, and the other five (8.8%) with multiple primary esophageal carcinomas. Most patients [55 of 57 (96.5%)] had squamous cell carcinoma, while two (3.5%) had adenocarcinoma. Of the 57 patients undergoing surgery, 22 (38.6%) received neoadjuvant therapy, including five (8.8%) treated with preoperative chemotherapy and 17 (29.8%) with preoperative chemoradiotherapy. The remaining 35 (61.4%) patients underwent surgery alone.

Surgery

A total of 56 (98.2%) patients received combined thoracoscopic and laparoscopic esophagectomy (McKeown's procedure) with esophageal reconstruction using the

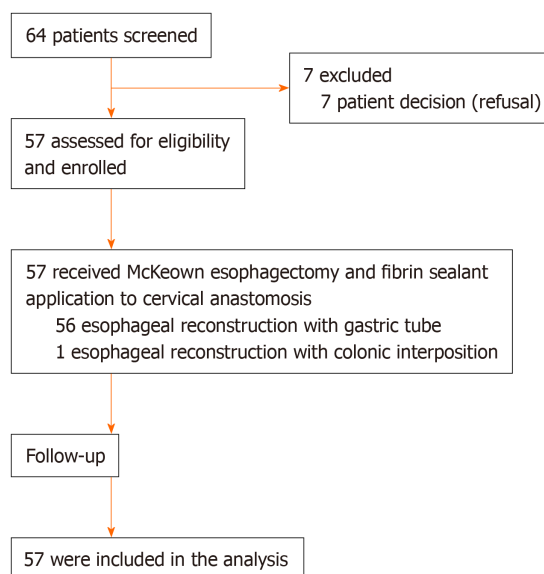


Figure 2 Trial profile.

gastric tube, and one (1.8%) underwent McKeown esophagectomy with colonic interposition by thoracoscopy plus open laparotomy. Most patients [56 (98.2%)] received R0 resection, while one (1.8%) underwent R2 resection because of tumor invasion of the thoracic aorta. The average (SD) operating time was 240.0 (\pm 35.9) min. Blood loss was generally minimal with a mean of 78.9 (\pm 44.3) mL. An average of 32.7 (\pm 11.6) lymph nodes were dissected. With respect to the distribution of pathologic stage grouping, pathological complete response was achieved in eight (36.4%) of the 22 patients receiving neoadjuvant therapy, and more details are shown in Table 2.

Outcomes

Three (5.3%) of the 57 patients experienced AL within the first 3 mo after operation (Table 3). Among them, one (1.8%) patient was diagnosed with gastric fistula confirmed by EGD 8 d after surgery (Supplementary Figure 1), and recovered within 18 d with conservative treatment. The other two (3.5%) were suspected of having AL with visible loss of saliva through the cervical wound after oral intake for a few days, and were finally confirmed with esophagogastric AL. In the first case, AL was detected and confirmed by EGD 10 d after surgery, while the extravasation of water-soluble contrast during a swallow study 21 d after surgery confirmed AL in the second. Both patients recovered after conservative treatment within 28 and 14 d, respectively. The remaining 54 patients were confirmed to be free from AL by contrast esophagography or EGD, and resumed oral intake without abnormal symptoms or signs. At the data cutoff, no more patients were diagnosed with AL. Additionally, none of the three patients with esophagogastric AL or gastric fistula had received neoadjuvant treatment before surgery.

Postoperative complication rate was 49.1% (28 of 57). The incidence of major and minor complications was 17.5% and 31.6% (10 and 18 of 57), respectively (Supplementary Table 1 and Table 2). The most prevalent complications were arrhythmia [11 (19.3%)] and recurrent nerve injury [10 (17.5%)] (Table 3). One (1.8%) patient was diagnosed with mild anastomotic stricture through EGD 55 d after surgery, and recovered after taking endoscopic dilatation. No adverse events related to FS were recorded, and no deaths occurred within 90 d after surgery.

The median duration of postoperative nasogastric tube placement was 1 d (IQR: 1.0-2.0) (Figure 3), and the median time to resume oral feeding after operation was 8 d (IQR: 7.0-9.0). The majority of patients began oral intake on postoperative day 7 or 8 routinely after confirming the absence of anastomotic leakage by contrast esophagography. However, 17 (29.8%) of the 57 patients delayed undergoing contrast esophagography and postponed oral feeding for different reasons. Among them, five (8.8%) patients delayed oral feeding because the testing facilities stopped working on weekends, while the remaining 12 were diagnosed with postoperative contraindications to oral feeding, including six with thoracic lymphorrhea cured by medical treatment, four with respiratory failure, one with gastric fistula, and one with chylothorax cured through surgical treatment. Furthermore, the median postoperative hospital stay duration was 11 d (IQR: 9.0-12.0).

Table 1 Baseline patient characteristics, *n* (%)

Variable	<i>n</i> = 57
Age, yr (median and range)	61 (41-75)
Sex	
Male	49 (86.0)
Female	8 (14.0)
BMI	
BMI < 24	46 (80.7)
BMI ≥ 24	11 (19.3)
Location of tumor	
Upper	4 (7.0)
Middle	20 (35.1)
Lower	23 (40.4)
Esophagogastric junction	5 (8.8)
Multiple primary tumor	5 (8.8)
Histology	
Squamous cell carcinoma	55 (96.5)
Adenocarcinoma	2 (3.5)
Differentiation	
Poor	13 (22.8)
Moderate	33 (57.9)
Well	2 (3.5)
Unknown	9 (15.8)
Clinical T stage	
cT1	3 (5.3)
cT2	19 (33.3)
cT3	34 (59.6)
cT4	1 (1.8)
Clinical N stage	
N0	24 (42.1)
N1	19 (33.3)
N2	9 (15.8)
N3	5 (8.8)
Clinical stage group	
I	2 (3.5)
II	28 (49.1)
III	21 (36.8)
IVA	6 (10.5)
Therapy	
Surgery and neoadjuvant chemotherapy	5 (8.8)
Surgery and neoadjuvant chemoradiotherapy	17 (29.8)
Surgery alone	35 (61.4)

BMI: Body mass index.

At the data cutoff point, eight (14.3%) of 56 patients who achieved R0 resection had tumor recurrence or had died, among whom two were found with supraclavicular lymph node metastases, two with mediastinal lymph node metastases, and four with distant metastases. Of the 57 patients who underwent resection, one (1.8%) died as a result of disease progression 189 d after surgery. The disease-free survival rate in patients with R0 resection was 79.5% at one year. The 1-year overall survival rate of the whole group was 98.2%. At present, both the median disease-free survival and overall survival have not yet been reached.

Table 2 Distribution of pathologic stage groups after surgery, *n* (%)

Pathologic stage group	<i>n</i> = 57
Surgery alone	
IB	6 (10.5)
IIA	13 (22.8)
IIB	5 (8.8)
IIIA	2 (3.5)
IIIB	8 (14.0)
IVA	1 (1.8)
Neoadjuvant therapy	
I	11 (19.3)
II	1 (1.8)
IIIA	4 (7.0)
IIIB	6 (10.5)

DISCUSSION

To our knowledge, this is the first phase II clinical study to assess the efficacy of FS in preventing AL post-esophagectomy in patients with resectable EC or EJC. Only three (5.3%) patients developed AL within the first 3 mo after operation. The incidences of anastomotic stricture and other major postoperative complications were 1.8% and 17.5%, respectively. No death occurred within 90 d after surgery. These results indicated that the intraoperative application of FS could probably prevent AL effectively with satisfactory safety.

This study was carried out based on the results of previous clinical studies regarding the prophylactic role of tissue adhesives in preventing AL in esophageal surgery^[13-16]. In those studies, the intraoperative use of FS after esophagectomy appeared safe and feasible^[13-17]. Thus, we carried out this phase II clinical trial in patients with resectable EC or EJC to further assess the efficacy of FS. We have previously reported an AL rate of 14.9% prior to using FS in our institution^[10]. The current study was designed to detect a 10% reduction in the incidence of postoperative AL in favor of the use of FS after esophagectomy, as compared with the expected AL rate based on our previous study (5% *vs* 15%)^[10]. The final results showed that the rate of postoperative AL was further reduced in the current study, and the outcome was better than that of previously reported series with esophagectomy alone (10.6%-26.1%)^[7-10].

A variety of modified anastomotic techniques for esophagectomy have been described with the intention of minimizing the risk of postoperative AL^[21-25]. However, the results are inconsistent, and the optimal technique remains a matter of debate^[21-25]. Sun *et al*^[23] reported and compared a novel embedded three-layer cervical esophagogastric anastomosis with traditional cervical anastomosis with respect to the incidence of postoperative complications in 339 EC patients. The rate of esophageal AL was significantly lower with the newly reported anastomotic technique [2.4% (4 of 166)] than with the conventional two-layer anastomotic technique [7.5% (13 of 173), *P* = 0.031]. Chen *et al*^[22] reported that omentoplasty might contribute to the reduction of AL after esophagectomy. The researchers conducted a meta-analysis of three randomized controlled trials with a total of 633 patients. A significantly lower rate of postoperative AL was shown in the omentoplasty group (OR = 0.26, 95%CI: 0.14-0.52, *P* < 0.0001) than in the non-omentoplasty group. However, large variations were present^[21-25] when using modified anastomotic techniques, since the surgical procedures were complicated and technically demanding, and were therefore difficult to replicate in other centers. In the current study, FS was used to strengthen the esophagogastric or esophago-colic anastomosis in patients with EC or EJC who received standard McKeown esophagectomy with a circular stapled anastomosis. Compared with other modified techniques, the application of FS on the anastomosis was easily administrable, resulting in less variation in technique between surgeons with little added operative time.

There have been conflicting results from previous studies regarding the role of FS for both the prevention and treatment of AL^[11,12,17,26-28], especially in esophageal surgery. To date, four clinical studies have reported the role of tissue adhesives in sealing esophageal anastomosis^[13-16]. Upadhyaya *et al*^[13] conducted a prospective randomized controlled trial enrolling 45 infants who underwent esophagectomy for

Table 3 Postoperative complications, n (%)

Postoperative complication	n = 57
Anastomotic leakage	3 (5.3)
Esophagogastric anastomosis ¹	2 (3.5)
Gastric stump ²	1 (1.8)
Anastomotic stricture	1 (1.8)
Arrhythmia	11 (19.3)
Laryngeal nerve injury	10 (17.5)
Pneumonia	8 (14.0)
Lymphorrhea	6 (10.5)
Heart failure	6 (10.5)
Respiratory failure	4 (7.0)
ARDS	3 (5.3)
Aerothorax	3 (5.3)
Pyothorax	1 (1.8)
Atelectasis	1 (1.8)
Chylothorax	1 (1.8)
Major complications	10 (17.5)
Minor complications	18 (31.6)

¹Full thickness gastrointestinal defects were detected at the esophagogastric anastomosis.

²Total parietal defect was detected at the staple line of gastric stump. ARDS: Acute respiratory distress syndrome.

congenital esophageal atresia with tracheoesophageal fistula. FS (Tisseel®) was used as reinforcement on a primary end-to-end esophageal anastomosis in the study group. The AL rate was only 9.1% (2/22), compared to 43% (10/23) in the control group ($P = 0.017$). Saldana-Cortes *et al*^[14] investigated the use of FS (Quixil®) in children after caustic esophageal injury. A colon interposition was used as the reconstruction substitute for the esophagus. Postoperative cervical anastomotic dehiscence and leakage were observed in 28.5% of patients who received FS (study group) and 50% in the control group, but the difference was not significant ($P = 0.17$). However, these studies were carried out in children with esophageal atresia or caustic esophageal injury. The benefit of FS as an anastomotic sealant to prevent AL after esophagectomy for EC has been questioned. So, in the present study, patients with EC or EJC were recruited, which differed from the design of Upadhyaya's and Saldana-Cortes's studies, in which patients with rare esophageal diseases were enrolled. On that point, only two feasibility studies have reported the use of FS to prevent AL in esophageal surgery for EC^[15,16]. Haverkamp *et al*^[15] published a pilot study to evaluate the feasibility of applying fibrin coated collagen patches (Tachosil®) to esophageal anastomosis. A total of 11 patches were successfully applied to the cervical esophagogastric anastomoses. AL occurred in two (18.2%) out of 11 patients. It was concluded that the application of Tachosil® to esophageal anastomosis was technically feasible. Plat *et al*^[16] also reported a similar feasibility study focusing on the application of autologous fibrin sealant to esophageal anastomoses. That study enrolled 15 patients with EC and reached a similar conclusion. Thus, the application of FS to esophageal anastomosis for EC is safe and technically feasible according to these previous studies. Despite this, both were pilot studies, and the sample size was relatively small. Moreover, the protective effects of FS in the prevention of AL after esophagectomy still needed to be verified. In this phase II clinical trial, we prospectively enrolled 57 patients, all of whom received standard McKeown esophagectomy and perioperative sealing with FS, to investigate the use of FS as an anastomotic sealant in patients with EC or EJC. The rate of AL was significantly decreased compared with that previously reported^[13-16]. Thus, safety and efficacy were favorable.

There were several factors that might have contributed to the promoted anastomotic healing due to FS observed in this study. First, FS mainly consists of thrombin and fibrinogen, which form a stable fibrin clot by stimulating the final pathway of the coagulation cascade. The fibrin clot will form a gel-like material on the surface of surgical wounds, which can not only directly block the tissue defect, but also promote wound healing by using the fibrin network as the matrix where

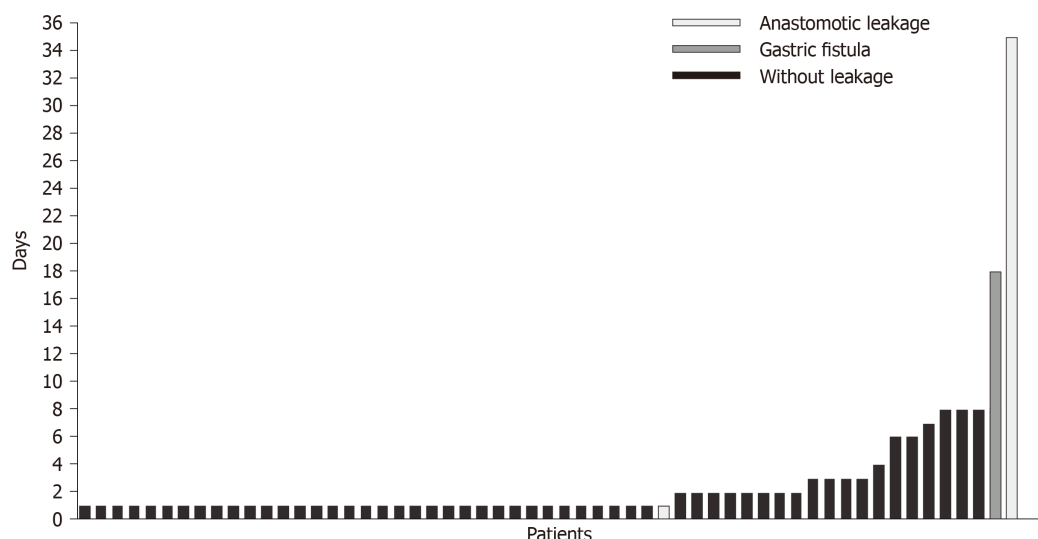


Figure 3 Postoperative nasogastric tube placement time.

fibroblasts and capillary endothelial cells can proliferate to form granulation^[11,29]. Second, FS could provide additional benefits for anastomotic healing by increasing the maturation process of granulation tissue during the first few days following surgery^[12,30]. Indeed, in Holmer's study^[30], higher mRNA levels of collagen types I and III, along with augmentation of granulation, were found in a rat model of anastomosis sutured with collagen fleece. Furthermore, since AL usually results from a preceding microleakage, a watertight esophageal anastomosis may be achieved by additional sealing with FS, leading to a lower occurrence of AL after esophageal surgery^[14,17].

This study had some limitations. Patients with poorer performance status or a long history of diabetes and older patients were excluded, so the applicability of this modified technique in these patients requires additional study. Moreover, most tumors included in our study were squamous cell carcinoma of the thoracic esophagus, which differs from the histological prevalence of EC in Western countries.

Of note, this trial is a single-arm study that compared the results against the AL rates from large population studies. Hence, the generalizability of our results should be considered with caution. A randomized, phase III clinical trial comparing the application of FS after esophagectomy with esophageal surgery without sealant application in patients with resectable EC or EJC is underway (NCT03847857). In addition, due to the large variability of FS regimens, including in physicochemical characteristics, the strength of adhesive joint, *etc.*, new types of adhesives with special properties that are especially suitable for esophageal anastomotic sealing need to be synthesized and investigated in the future.

In conclusion, our study showed that perioperative sealing with FS appears to be safe and may prevent AL after McKeown esophagectomy in patients with resectable EC or EJC. Further phase III trials are warranted to confirm our findings.

ARTICLE HIGHLIGHTS

Research background

Esophagectomy is the primary treatment for localized esophageal or esophagogastric junction cancer (EC or EJC). Postoperative anastomotic leakage (AL) remains problematic. The use of fibrin sealant (FS) may improve the strength of esophageal anastomosis and reduce the incidence of AL.

Research motivation

Previous pilot studies showed that the application of FS to esophageal anastomosis for EC is safe and technically feasible.

Research objectives

This study aimed to assess the efficacy and safety of applying FS to prevent AL in patients with EC or EJC.

Research methods

In this phase II study, the efficacy and safety of FS application were evaluated in 57 patients with resectable EC or EJC undergoing McKeown esophagectomy.

Research results

All patients received McKeown esophagectomy with intraoperative application of FS. Three (5.3%) of the 57 patients developed AL within the first 3 mo after operation, including two (3.5%) with esophagogastric AL and one (1.8%) with gastric fistula. The use of FS was associated with a low incidence of postoperative morbidity and mortality, and led to an improved outcome with rapid recovery and shortened hospital stay duration.

Research conclusions

Perioperative sealing with porcine FS appears safe and may prevent AL after esophagectomy in patients with resectable EC or EJC.

Research perspectives

The favorable benefits of fibrin sealant support further investigation in phase III trials and implementation in clinical practice.

ACKNOWLEDGEMENTS

The authors thank all the patients and their families who participated in this study. The authors thank Yi Hu, Guang-Yu Luo, and Jing-Xian Shen from the Independent Data Monitoring Committee, and Xiao-Dong Su, Ying Guo, and Zhi-Qiang Wang, who compose the Independent Image Committee, for their support. The authors thank Ji-Bin Li for his help with the statistical analysis and interpretation.

REFERENCES

- Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; **68**: 394-424 [PMID: 30207593 DOI: 10.3322/caac.21492]
- Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, Jemal A, Yu XQ, He J. Cancer statistics in China, 2015. *CA Cancer J Clin* 2016; **66**: 115-132 [PMID: 26808342 DOI: 10.3322/caac.21338]
- Ng T, Vezeridis MP. Advances in the surgical treatment of esophageal cancer. *J Surg Oncol* 2010; **101**: 725-729 [PMID: 20512949 DOI: 10.1002/jso.21566]
- Biere SS, Maas KW, Cuesta MA, van der Peet DL. Cervical or thoracic anastomosis after esophagectomy for cancer: a systematic review and meta-analysis. *Dig Surg* 2011; **28**: 29-35 [PMID: 21293129 DOI: 10.1159/000322014]
- Jones CE, Watson TJ. Anastomotic Leakage Following Esophagectomy. *Thorac Surg Clin* 2015; **25**: 449-459 [PMID: 26515945 DOI: 10.1016/j.thorsurg.2015.07.004]
- Turrentine FE, Denlinger CE, Simpson VB, Garwood RA, Guerlain S, Agrawal A, Friel CM, LaPar DJ, Stukenborg GJ, Jones RS. Morbidity, mortality, cost, and survival estimates of gastrointestinal anastomotic leaks. *J Am Coll Surg* 2015; **220**: 195-206 [PMID: 25592468 DOI: 10.1016/j.jamcollsurg.2014.11.002]
- Kassis ES, Kosinski AS, Ross P Jr, Koppes KE, Donahue JM, Daniel VC. Predictors of anastomotic leak after esophagectomy: an analysis of the society of thoracic surgeons general thoracic database. *Ann Thorac Surg* 2013; **96**: 1919-1926 [PMID: 24075499 DOI: 10.1016/j.athoracsur.2013.07.119]
- Takeuchi H, Miyata H, Gotoh M, Kitagawa Y, Baba H, Kimura W, Tomita N, Nakagoe T, Shimada M, Sugihara K, Mori M. A risk model for esophagectomy using data of 5354 patients included in a Japanese nationwide web-based database. *Ann Surg* 2014; **260**: 259-266 [PMID: 24743609 DOI: 10.1097/SLA.0000000000000644]
- van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP, Richel DJ, Nieuwenhuijzen GA, Hospers GA, Bonenkamp JJ, Cuesta MA, Blaisse RJ, Busch OR, ten Kate FJ, Creemers GJ, Punt CJ, Plukker JT, Verheul HM, Spillenaar Bilgen EJ, van Dekken H, van der Sangen MJ, Rozema T, Biermann K, Beukema JC, Piet AH, van Rij CM, Reinders JG, Tilanus HW, van der Gaast A; CROSS Group. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012; **366**: 2074-2084 [PMID: 22646630 DOI: 10.1056/NEJMoa1112088]
- Tan Z, Ma G, Zhao J, Bella AE, Rong T, Fu J, Meng Y, Luo K, Situ D, Lin P. Impact of thoracic recurrent laryngeal node dissection: 508 patients with tri-incisional esophagectomy. *J Gastrointest Surg* 2014; **18**: 187-193 [PMID: 24241966 DOI: 10.1007/s11605-013-2411-2]
- Duarte AP, Coelho JF, Bordado JC, Cidade MT, Gil MH. Surgical adhesives: Systematic review of the main types and development forecast. *Prog Polym Sci* 2012; **37**: 1031-1050 [DOI: 10.1016/j.progpolymsci.2011.12.003]
- Vakalopoulos KA, Daams F, Wu Z, Timmermans L, Jeekel JJ, Kleinrensink GJ, van der Ham A, Lange JF. Tissue adhesives in gastrointestinal anastomosis: a systematic review. *J Surg Res* 2013; **180**: 290-300 [PMID: 23384970 DOI: 10.1016/j.jss.2012.12.043]
- Upadhyaya VD, Gopal SC, Gangopadhyaya AN, Gupta DK, Sharma S, Upadhyaya A, Kumar V, Pandey A. Role of fibrin glue as a sealant to esophageal anastomosis in cases of congenital esophageal atresia with tracheoesophageal fistula. *World J Surg* 2007; **31**: 2412-2415 [PMID: 17917772 DOI: 10.1007/s00268-007-9244-7]
- Saldaña-Cortés JA, Larios-Arceo F, Prieto-Díaz-Chávez E, De Buen EP, González-Mercado S, Alvarez-Villaseñor AS, Prieto-Aldape MR, Fuentes-Orozco C, González-Ojeda A. Role of fibrin glue in the prevention of cervical leakage and strictures after esophageal reconstruction of caustic injury. *World J Surg* 2009; **33**: 986-993 [PMID: 19234736 DOI: 10.1007/s00268-009-9949-x]
- Haverkamp L, Ruurda JP, van Hillegersberg R. Technical Feasibility of TachoSil Application on Esophageal Anastomoses. *Gastroenterol Res Pract* 2015; **2015**: 534080 [PMID: 26101523 DOI: 10.1155/2015/534080]
- Plat VD, Bootsma BT, van der Wielen N, van der Peet DL, Daams F. Autologous Activated Fibrin Sealant

- for the Esophageal Anastomosis: A Feasibility Study. *J Surg Res* 2019; **234**: 49-53 [PMID: [30527497](#) DOI: [10.1016/j.jss.2018.08.049](#)]
- 17 **Plat VD**, Bootsma BT, van der Wielen N, Straatman J, Schoonmade LJ, van der Peet DL, Daams F. The role of tissue adhesives in esophageal surgery, a systematic review of literature. *Int J Surg* 2017; **40**: 163-168 [PMID: [28285057](#) DOI: [10.1016/j.ijsu.2017.02.093](#)]
- 18 **Grimminger PP**, Goense L, Gockel I, Bergeat D, Bertheuil N, Chandramohan SM, Chen KN, Chon SH, Denis C, Goh KL, Gronnier C, Liu JF, Meunier B, Naftaux P, Pirchi ED, Schiesser M, Thieme R, Wu A, Wu PC, Buttar N, Chang AC. Diagnosis, assessment, and management of surgical complications following esophagectomy. *Ann N Y Acad Sci* 2018; **1434**: 254-273 [PMID: [29984413](#) DOI: [10.1111/nyas.13920](#)]
- 19 **Low DE**, Alderson D, Ceconello I, Chang AC, Darling GE, D'Journo XB, Griffin SM, Hölscher AH, Hofstetter WL, Jobe BA, Kitagawa Y, Kucharczuk JC, Law SY, Lerut TE, Maynard N, Pera M, Peters JH, Pramesh CS, Reynolds JV, Smithers BM, van Lanschot JJ. International Consensus on Standardization of Data Collection for Complications Associated With Esophagectomy: Esophagectomy Complications Consensus Group (ECCG). *Ann Surg* 2015; **262**: 286-294 [PMID: [25607756](#) DOI: [10.1097/SLA.0000000000001098](#)]
- 20 **Dindo D**, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; **240**: 205-213 [PMID: [15273542](#) DOI: [10.1097/01.sla.0000133083.54934.ae](#)]
- 21 **Takemura M**, Yoshida K, Fujiwara Y. Modified triangulating stapling technique for esophagogastrotomy after esophagectomy for esophageal cancer. *Surg Endosc* 2013; **27**: 1249-1253 [PMID: [23093236](#) DOI: [10.1007/s00464-012-2586-8](#)]
- 22 **Chen L**, Liu F, Wang K, Zou W. Omentoplasty in the prevention of anastomotic leakage after oesophagectomy: a meta-analysis. *Eur J Surg Oncol* 2014; **40**: 1635-1640 [PMID: [25220157](#) DOI: [10.1016/j.ejso.2014.07.038](#)]
- 23 **Sun HB**, Li Y, Liu XB, Zhang RX, Wang ZF, Zheng Y, Qin JJ, Li HM, Chen XK, Wu Z. Embedded Three-Layer Esophagogastric Anastomosis Reduces Morbidity and Improves Short-Term Outcomes After Esophagectomy for Cancer. *Ann Thorac Surg* 2016; **101**: 1131-1138 [PMID: [26687140](#) DOI: [10.1016/j.athoracsur.2015.09.094](#)]
- 24 **Ishibashi Y**, Fukunaga T, Mikami S, Oka S, Kanda S, Yube Y, Kohira Y, Enomoto T, Otsubo T. Triple-stapled quadrilateral anastomosis: a new technique for creation of an esophagogastric anastomosis. *Esophagus* 2018; **15**: 88-94 [PMID: [29892931](#) DOI: [10.1007/s10388-017-0599-z](#)]
- 25 **Zhou D**, Liu QX, Deng XF, Zheng H, Lu X, Dai JG, Jiang L. Anastomotic reinforcement with omentoplasty reduces anastomotic leakage for minimally invasive esophagectomy with cervical anastomosis. *Cancer Manag Res* 2018; **10**: 257-263 [PMID: [29445302](#) DOI: [10.2147/cmar.s145917](#)]
- 26 **Lippert E**, Klebl FH, Schweller F, Ott C, Gelbmann CM, Schölmerich J, Endlicher E, Kullmann F. Fibrin glue in the endoscopic treatment of fistulae and anastomotic leakages of the gastrointestinal tract. *Int J Colorectal Dis* 2011; **26**: 303-311 [PMID: [21190028](#) DOI: [10.1007/s00384-010-1104-5](#)]
- 27 **Wu X**, Ren J, Wang G, Wang J, Wang F, Fan Y, Li Y, Han G, Zhou Y, Song X, Quan B, Yao M, Li J. Evaluating the use of fibrin glue for sealing low-output enterocutaneous fistulas: study protocol for a randomized controlled trial. *Trials* 2015; **16**: 445 [PMID: [26445823](#) DOI: [10.1186/s13063-015-0966-9](#)]
- 28 **Nguyen NT**, Nguyen CT, Stevens CM, Steward E, Paya M. The efficacy of fibrin sealant in prevention of anastomotic leak after laparoscopic gastric bypass. *J Surg Res* 2004; **122**: 218-224 [PMID: [15555621](#) DOI: [10.1016/j.jss.2004.05.005](#)]
- 29 **Pantelis D**, Beissel A, Kahl P, Wehner S, Vilz TO, Kalff JC. The effect of sealing with a fixed combination of collagen matrix-bound coagulation factors on the healing of colonic anastomoses in experimental high-risk mice models. *Langenbecks Arch Surg* 2010; **395**: 1039-1048 [PMID: [20680329](#) DOI: [10.1007/s00423-010-0703-5](#)]
- 30 **Holmer C**, Praechter C, Mecklenburg L, Heimesaat M, Rieger H, Pohlen U. Anastomotic stability and wound healing of colorectal anastomoses sealed and sutured with a collagen fleece in a rat peritonitis model. *Asian J Surg* 2014; **37**: 35-45 [PMID: [23978425](#) DOI: [10.1016/j.asjsur.2013.07.008](#)]



Published by Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: <https://www.f6publishing.com/helpdesk>
<https://www.wjgnet.com>

