Trials

STUDY PROTOCOL

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Whole stomach versus narrow gastric tube reconstruction after esophagectomy for esophageal cancer (ATHLETE trial): study protocol for a randomized controlled trial

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Abstract

Background There are two types of methods of creating a gastric conduit after esophagectomy for patients with esophageal cancer: narrow gastric tube reconstruction or whole stomach reconstruction. Whole stomach reconstruction with good blood perfusion was reported in a prospective cohort study to be safe and that it has the possibility to prevent anastomotic leakage (AL). We therefore planned a randomized controlled phase III study to investigate the superiority of whole stomach reconstruction over narrow gastric tube reconstruction after esophagectomy for esophageal cancer.

Methods This is a single center, two-arm, open-label, randomized phase III trial. We calculated that 65 patients in each arm of this study and total study population of 130 patients are required according to our historical data on narrow gastric tube reconstruction and prospective data on whole stomach reconstruction. In the narrow gastric tube group, a 3.5-cm-wide gastric tube is made along the greater curvature of the stomach using linear staplers. Otherwise, in the whole stomach group, after the lymphadenectomy of the lesser curvature and No.2, the stomach is cut just below the esophagogastric junction using a linear stapler. The primary endpoint of this study is the incidence of AL. Secondary endpoints are the occurrence rate of anastomotic stenosis, the occurrence rate of pneumonia, the occurrence rate of all postoperative complications, the occurrence rate of reflux esophagitis, quality of life evaluation by EORTC QLQ-C30 and EORTC OES-18, nutritional evaluation, the amount of blood loss, postoperative hospital stays, and blood flow evaluation. Complications are evaluated using the Clavien-Dindo classification (version 2.0), and those of grade II or higher are considered to be postoperative complications.

Discussion If the optimal method for creating a gastric conduit after esophagectomy is clarified, it may be possible to contribute to improving short-term and long-term surgical outcomes for patients undergoing surgery for esophageal cancer.

Trial registration The protocol of ATHLETE trial was registered in the UMIN Clinical Trials Registry as UMIN000050677 (http://www.umin.ac.jp/ctr/index.htm). Date of registration: March 26, 2023. Date of first participant enrollment: March 27, 2023.

Keywords Esophageal cancer, Esophagectomy, Whole stomach, Gastric tube

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Background

Radical esophagectomy for esophageal cancer is extremely invasive and has a higher incidence of complications than other gastrointestinal surgeries. In particular, anastomotic leakage (AL) after gastric tube reconstruction, the most commonly used reconstruction, has a significant impact on the postoperative course and can sometimes lead to serious complications or mortality [1–4].

Poor blood perfusion of the gastric conduit has been found in recent years to be strongly associated with AL [5, 6]. The methods of creating a gastric conduit, those using the narrow gastric tube and those using the whole stomach, can affect blood perfusion [7, 8]. Each method has both pros and cons. The biggest advantage of narrow gastric tube reconstruction is that it is possible to create a long gastric conduit, but it has the disadvantage that the blood network within the stomach wall is cut off, especially in lesser curvature with rich network. Meanwhile, whole stomach reconstruction has the advantage that the entire blood network within the gastric wall is maintained, but there is sometimes difficulty in pulling up the gastric conduit to the neck without the Kocher maneuver [9]. A small scale randomized controlled trial (RCT) with 22 patients in each group was reported regarding these two methods of creating a gastric conduit [10]. The rate of AL in the narrow gastric tube group was 22.7%, whereas that in the whole stomach group was 4.5%. However, the sample size was small, and no significant difference was found between the two groups. In addition, retrospective studies have reported that the incidence of AL in whole stomach reconstruction is less than 1%, so this reconstruction method could contribute to preventing AL [11]. Therefore, to assess the feasibility and safety, we performed a prospective cohort study of whole stomach reconstruction after esophagectomy between August 2022 and March 2023. Whole stomach reconstruction was performed in 20 consecutive patients, and there were no occurrences of AL. As a historical control, the rate of AL in cases of narrow gastric tube reconstruction performed in our department over the past 5 years was 22.9% [9]. Whole stomach reconstruction with good blood perfusion is thus considered to be safe and it may prevent AL after esophagectomy for patients with esophageal cancer.

Therefore, we planned the RCT (ATHLETE trial) with a sufficient sample size to investigate the potential superiority of whole stomach reconstruction over narrow gastric tube reconstruction after esophagectomy for esophageal cancer.

Methods and design

Aim

In this study, we will compare the incidence of AL after narrow gastric tube reconstruction with that after whole stomach reconstruction. In addition, we will evaluate complications such as anastomotic stenosis, perioperative course, body weight change, and quality of life (QOL) after both reconstruction methods in the short and middle term. Ultimately, we seek to clarify the optimal method of creating a gastric conduit for reconstruction after esophagectomy.

Study setting

This is a single center, two-arm, open-label, randomized phase III trial. This study will be conducted at Wakayama Medical University Hospital (WMUH). This protocol version is 1.0 which was enacted on January 19, 2023.

Endpoints

The primary endpoint of this study is the incidence of AL, which is assessed from the end of surgery to the first postoperative discharge. Secondary endpoints are the occurrence rate of anastomotic stenosis, the occurrence rate of pneumonia, the occurrence rate of all postoperative complications, the occurrence rate of reflux esophagitis, QOL evaluation by EORTC QLQ-C30 and EORTC OES-18, nutritional evaluation, the amount of blood loss, postoperative hospital stays, and blood flow evaluation. Complications are evaluated using the Clavien-Dindo classification (version 2.0) from surgery until the first postoperative discharge [12]; those of grade II or higher are considered to be postoperative complications. This examination schedule is shown in Fig. 1. EORTC QLQ-C30 is a 30-item questionnaire, including five domains related to physical, role, cognitive, psychological, and social aspects, as well as scales related to several symptoms (fatigue, pain, nausea, vomiting) with measurement of global QOL. EORTC OES-18 is an 18-item questionnaire used to assess the QOL of patients with esophageal cancer [13]. Esophageal reflux is evaluated by endoscopic examination using the Los Angeles classification [14]. Nutritional evaluation is assessed by prognostic nutritional index = 10 × albumin (g/dl) + 0.005 × total lymphocyte count (/μl) and controlling nutritional status score [15]. Blood perfusion of a gastric conduit is assessed by indocyanine green (ICG), as in a previous study [6, 16]. Five milligrams of ICG dye (Diagnogreen, Daiichi-Sankyo Pharmaceutical, Tokyo, Japan) is administered intravenously following formation of the gastric conduit. Blood perfusion of the gastric wall is evaluated for 1 to 60 s after ICG injection using an infrared ray imaging system (PDE; Hamamatsu Photonics K.K, Hamamatsu, Japan).

Study design and statistical analysis

This randomized study is designed to confirm our hypothesis that whole stomach reconstruction is

	Preoperative phase	Operation	~Discharge	Postoperative phase		
Date	Within 28days	0		3months	6months	12months
Obtaining consent	✓					
Preoperative information	✓					
Blood examination	✓			✓	✓	✓
Registration	✓					
Allocation		✓				
Operative information		✓				
Postoperative complications			✓			
Postoperative coarse			✓			
Late complications				✓	✓	✓
Upper gastrointestinal endoscopy						✓
Physical findings	✓			✓	✓	✓
Quality of life	✓					✓

Fig. 1 The ATHLETE trial examination schedule

superior to narrow gastric tube reconstruction in terms of the lower occurrence of AL. If, as expected, the data demonstrate superiority of whole stomach reconstruction over narrow gastric tube reconstruction, whole stomach reconstruction will be considered the optimum method of creating gastric conduit after esophagectomy for thoracic esophageal cancer. The sample size to predict the patients' number for statistical validity is based on our retrospective data of narrow gastric tube reconstruction from between January 2018 and July 2022 ($n=183$) and prospective data of whole stomach reconstruction from between August 2022 and March 2023 ($n=20$) [9]. According to this data, the incidence rate of AL after narrow gastric tube reconstruction was 22.9%. According to this study and that of another previous study, the incidence rate of 18% in the narrow gastric tube group was estimated [17]. As this incidence rate in the whole stomach group was 0% in the prospective cohort study, the incidence rate of AL in the whole stomach group according to the other previous study was expected to be 3% [9, 10]. We calculated that 64 patients are required in each arm of this study with a significance $\alpha=0.05$ and a power of $(1-\beta)=0.8$. The sample size of this study was designed to be two-sided. Anticipating follow-up loss, we calculated that 65 patients are required in each arm of this study, a total study population of 130 patients. We follow up every patient at our university hospital. So, the dropping out rate for follow-up is considered to be very low. For all efficacy evaluations, analysis of the full analysis set will be the primary analysis. For reference, analysis of the per protocol set will also be performed. Safety analysis will be performed on all treated cases.

Since the analysis of secondary endpoints is exploratory, no adjustment for multiplicity will be made. Although between-group comparisons will be made where necessary, statistical power is not guaranteed by the study design. Regarding the incidence of anastomotic stenosis, aspiration pneumonia, postoperative complications, and reflux esophagitis, the incidence and proportion of each group will be calculated, along with 95% confidence intervals. Clopper and Pearson's exact confidence intervals will be used to construct the 95% confidence intervals. Odds ratios and 95% confidence intervals will also be calculated. To summarize QOL, medians and interquartile ranges will be calculated for each group. Only statistical analysts will have access to the dataset.

Eligibility criteria

Inclusion criteria

1) Patients with thoracic esophageal cancer whose tumor does not extend to the cervical esophagus.

2) Patients among whom the stomach is used as a reconstructed organ and who undergo reconstruction by either the posterior mediastinal route or the retrosternal route.
3) Patients undergoing anastomosis in the neck.
4) Patients who undergo 2-field or 3-field lymph node dissection.
5) Patients aged between 18 and 85 years old at the time of enrollment.
6) Patients who have provided informed consent.

Exclusion criteria

1) Patients judged to be unable to undergo either narrow gastric tube or whole stomach reconstruction due to intraoperative findings.
2) Patients with tumor invasion into the stomach.
3) Patients with serious complications (interstitial pneumonia or pulmonary fibrosis, difficult-to-control diabetes, ischemic heart disease requiring treatment, heart failure).
4) Patients with moderate or severe hepatic or renal dysfunction.
5) Patients with cirrhosis or active hepatitis.
6) Patients undergoing dialysis.
7) Patients otherwise judged inappropriate for inclusion by the attending physician.

The principal investigator and co-investigators will adhere to the inclusion and exclusion criteria for subjects. Adverse events that are ongoing at the time of completion or discontinuation of the study will be followed up as much as possible until they have disappeared or improved. Prior to the start of the study, the principal investigator or co-investigator will provide the subjects with a clear explanation using an informed consent document and consent form. After obtaining consent from the subjects, data management and case handling will all be managed using the subject identification code or registration number, and a table corresponding to the subject identification code, registration number and name, as well as the consent form with the subject's name written on it will be securely stored in a lockable document storage facility.

Participating surgeons

The complication rate can be affected by the experience of the operating surgeon, which might bias results. To prevent surgeon bias, participating surgeons must satisfy the following criteria: (1) having experience of more than 20 cases of gastric conduit reconstruction, (2) having experience of totally more than 20 cases of laparoscopic or robotic gastrectomy for the gastric conduit reconstruction by the minimally invasive procedure, and (3) being a board-certified fellow of the Japanese Society of Gastroenterological Surgery.

Randomization

After confirming the eligibility criteria, registration is made by telephone to the central registry in WMUH. Study of each group is carried out using a series of consecutive numbers assigned by the WMUH central registry. After esophagectomy and lymph node dissection are completed, the principal investigator or co-investigator will ask the randomization officer to randomize the subjects. Patients are randomized to either the narrow gastric tube arm or whole stomach group arm by a minimization method balancing the arms by the reconstruction route (retrosternal route or posterior mediastinal route) which is an important factor to affect the occurrence of AL and neoadjuvant therapy (performed or not performed). The allocation to narrow gastric tube reconstruction or whole stomach reconstruction will be performed using the permutation block method. Protocol treatment will be considered complete when the anastomosis is completed. If it is determined after allocation that the assigned reconstruction is impossible, the patient will be considered an incompetent case of protocol treatment, and this will be noted in the case report, and an appropriate reconstruction method should be performed. In order to achieve the target number of enrollments within the period, screening of enrollable cases and investigation of all cases will be conducted.

Treatments

Patients with thoracic esophageal cancer undergo esophagectomy and mediastinal dissection with extensive lymphadenectomy. Abdominal lymphadenectomy and gastric tube reconstruction are performed either by open or laparoscopic or robotic procedure following the thoracic part. The stomach is maneuvered intracorporeally. In the narrow gastric tube group, a 3.5-cm-wide gastric tube is made along the greater curvature of the stomach using linear-stapling devices (Fig. 2). The staple edge is embedded by suturing. Otherwise, in whole stomach group, after the stomach is pulled out extracorporeally, the lymph nodes of the lesser curvature and No.2 station are dissected. The stomach is cut just below the esophagogastric junction using a linear stapler, as previously reported [9]. Kocher maneuver is a necessary procedure to make it easier to pull up the gastric conduit. So, if it is difficult to pull up the gastric conduit, it is permitted to perform the Kocher

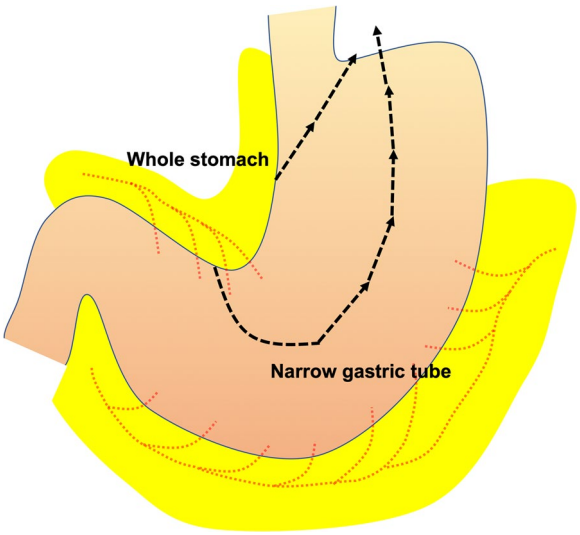

Fig. 2 Schema of two procedures: narrow gastric tube reconstruction and whole stomach reconstruction

maneuver. After the gastric conduit is covered with a nylon bag, it is carefully pulled up to the neck through the retrosternal route or posterior mediastinal route. The esophagogastrostomy is performed with hand-sewn Albert-Lembert anastomosis. Finally, the anastomosis site is pulled back into the mediastinum to be straight. A nasogastric tube is placed in the gastric conduit for all patients. A feeding tube is placed through the antrum to the jejunum in cases of the retrosternal route reconstruction, or directly into the jejunum in cases of the posterior mediastinum route reconstruction [18]. Although our preliminary prospective data of whole stomach reconstruction have not shown poor blood perfusion, it is possible that poor blood perfusion may be found [9]. In such cases, we can convert to a narrow gastric tube reconstruction. However, this conversion case should be excluded from the protocol set. If an adverse event occurs as a result of the research and causes health damage to a subject, the principal investigator or co-investigator will take the best possible measures, including appropriate medical treatment and other necessary measures. There are no specific regulations regarding treatment after surgery including postoperative adjuvant chemotherapy.

Follow-up

A detailed listing of the following procedures and items is shown in Fig. 1. Enteral feeding via a jejunostomy catheter for patients will be basically inserted for 2 or 3 months if they do not refuse an insertion. Patients will be discharged according to standard practice. All patients are followed up for more than 5 years or until death.

Physical assessment including body weight and body mass index, and blood examination about total protein, albumin, total cholesterol, triglycerides, and complete blood count will be performed every 3 months after surgery. Enhanced computed tomography scans of the chest and abdomen will be evaluated every 6 months during follow-up according the esophageal cancer practice guidelines 2022 edited by the Japan esophageal society [19]. The evidence of adjuvant therapy after neoadjuvant chemotherapy followed by radical esophagectomy is controversial. So, adjuvant therapy after surgery is not defined. Otherwise, postoperative nivolumab therapy is strongly recommended for cStage II or III esophageal cancer which failed to show a pathologic complete response after preoperative chemoradiotherapy plus surgery with radical resection [20].

Monitoring and interim analysis

Monitoring will confirm whether the human rights, safety, and welfare of patients are protected and whether the study is being conducted in compliance with the latest implementation plan and standard operating procedures. Monitoring will be based on facility visits and will be carried out regularly by monitoring staff. As a general rule, regular monitoring is performed once a year. The individual who performs monitoring in this study will compile the results of regular monitoring into a report and submit it to the research office and the principal investigator. No interim analysis is planned. Serious adverse events will be handled in accordance with Wakayama Medical University's Procedures for Response to Serious Adverse Events in Life Science and Medical Research Involving Human Subjects. The principal investigator will take appropriate action regardless of the causal relationship to the surgical procedure and will immediately report the details in writing to the Ethics Committee and the University President. If an unexpected serious adverse event occurs and a direct causal relationship to the research cannot be denied, the principal investigator will report it to the Ministry of Health, Labor and Welfare. If there are any changes to the implementation plan, the principal investigator must report this to the institutional review board and the president and obtain approval for the changes. Once the study is completed, the results will be published promptly in a peer-reviewed paper.

Discussion

Once AL occurs, the start of adjuvant chemotherapy may be delayed or cannot be started in cases of advanced cancer, and this may worsen the prognosis [3, 4]. In other words, there is an urgent need to

standardize gastric tube creation and reconstruction methods that can prevent serious complications and reduce the rate of AL. There is currently no clear evidence of differences between the two methods, so the decision to select the method concerned with the creation of the gastric conduit has depended on the surgeon's preference.

This RCT aims to make it possible to objectively evaluate postoperative complications such as AL and anastomotic stenosis, the perioperative course, and body weight changes between narrow gastric tube reconstruction and whole stomach reconstruction. If the optimal method of creation of a gastric conduit after esophagectomy is clarified, it may be possible to contribute to improving short-term and long-term surgical outcomes for patients undergoing surgery for esophageal cancer. Furthermore, the results may contribute to shortening the duration of hospital stays and reducing treatment-related expense.

This study is limited by it being conducted at a single institution. Due to the small sample size, findings from this trial do not allow established clinical application, but rather serve to inform the need for larger multicenter, phase III, RCTs on the advantage of whole stomach reconstruction for patients with esophageal cancer.

Trial status

Protocol version 1.0; January 2023.

The trial started and actively enrolling since March 27, 2023.

Primary completion: December 31, 2026 (approximate date when recruitment will be completed).

Abbreviations

AL	Anastomotic leakage
RCT	Randomized controlled trial
QOL	Quality of life

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-025-08823-9.

Additional file 1: Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 Checklist: recommended items to address in a clinical trial protocol and related documents.

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Authors' contributions

JK, KH, TG, ST, NF, TN, and SN designed the protocol and drafted the manuscript. TS performed the statistical analysis. TO and MK further aided in assessment and revision of the protocol and revised the manuscript. All authors read and approved the final version of the protocol.

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Data availability

Data sharing is not applicable to this article because no datasets had been generated or analyzed at the time of submission.

Declarations

Ethics approval and consent to participate

This study was approved by the Wakayama Medical University Institutional Review Board (approval number 3779). All procedures were undertaken in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and in accordance with the Helsinki Declaration of 1964 and later versions. All patients gave written informed consent in accordance with its guidelines.

Competing interests

None declared.

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References

1. D'Journo XB, Boulate D, Fourdrain A, Loundou A, van Berge Henegouwen MI, Gisbertz SS, et al. Risk prediction model of 90-day mortality after esophagectomy for cancer. JAMA Surg. 2021;156:836–45.
2. Kataoka K, Takeuchi H, Mizusawa J, Igaki H, Ozawa S, Abe T, et al. Prognostic impact of postoperative morbidity after esophagectomy for esophageal cancer: exploratory analysis of JCOG9907. Ann Surg. 2017;265:1152–7.
3. Kitadani J, Ojima T, Nakamura M, Hayata K, Katsuda M, Takeuchi A, et al. Impact of anastomotic leakage on survival for patients with thoracic esophageal cancer performed with esophagectomy followed by right colon interposition. J Gastrointest Surg. 2022;26:1090–2.
4. Markar S, Gronnier C, Duhamel A, Mabrut JY, Bail JP, Carrere N, et al. The impact of severe anastomotic leak on long-term survival and cancer recurrence after surgical resection for esophageal malignancy. Ann Surg. 2015;262:972–80.
5. Nishikawa K, Fujita T, Yuda M, Tanaka Y, Matsumoto A, Tanishima Y, et al. Quantitative assessment of blood flow in the gastric conduit with thermal imaging for esophageal reconstruction. Ann Surg. 2020;271:1087–94.
6. Ohi M, Toiyama Y, Mohri Y, Saigusa S, Ichikawa T, Shimura T, et al. Prevalence of anastomotic leak and the impact of indocyanine green fluorescein imaging for evaluating blood flow in the gastric conduit following esophageal cancer surgery. Esophagus. 2017;14:351–9.
7. Hayata K, Nakamori M, Nakamura M, Ojima T, Iwahashi M, Katsuda M, et al. Circular stapling versus triangulating stapling for the cervical esophagogastric anastomosis after esophagectomy in patients with thoracic esophageal cancer: a prospective, randomized, controlled trial. Surgery. 2017;162:131–8.
8. Ishikawa Y, Chang AC, Lin J, Orringer MB, Lynch WR, Lagisetty KH, et al. Wider gastric conduit morphology is associated with improved blood flow during esophagectomy. J Gastrointest Surg. 2023;27:845–54.
9. Kitadani J, Ojima T, Hayata K, Goda T, Takeuchi A, Tominaga S, et al. Impact of zero anastomotic leakage after esophagectomy followed by whole stomach reconstruction for esophageal cancer: prospective cohort study. Langenbecks Arch Surg. 2023;408:451.
10. Tabira Y, Sakaguchi T, Kuhara H, Teshima K, Tanaka M, Kawasuji M. The width of a gastric tube has no impact on outcome after esophagectomy. Am J Surg. 2004;187:417–21.
11. Yoshida K, Tanaka Y, Imai T, Sato Y, Hatanaka Y, Suetsugu T, et al. Subtotal stomach in esophageal reconstruction surgery achieves an anastomotic leakage rate of less than 1%. Ann Gastroenterol Surg. 2020;4:422–32.

12. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg. 2009;250:187–96.
13. Cavallin F, Pinto E, Saadeh LM, Alfieri R, Cagol M, Castoro C, et al. Health related quality of life after oesophagectomy: elderly patients refer similar eating and swallowing difficulties than younger patients. BMC Cancer. 2015;15:640.
14. Yano M, Sugimura K, Miyata H, Motoori M, Tanaka K, Omori T, et al. Randomized comparison of gastric tube reconstruction with and without duodenal diversion plus Roux-en-Y anastomosis after esophagectomy. Ann Surg. 2020;272:48–54.
15. Hikage M, Taniyama Y, Sakurai T, Sato C, Takaya K, Okamoto H, et al. The influence of the perioperative nutritional status on the survival outcomes for esophageal cancer patients with neoadjuvant chemotherapy. Ann Surg Oncol. 2019;26:4744–53.
16. Kitadani J, Hayata K, Goda T, Tominaga S, Fukuda N, Nakai T, et al. Risk reduction of severe anastomotic leakage by evaluation of blood perfusion using indocyanine green after minimally invasive esophagectomy followed by narrow gastric tube reconstruction. Surg Laparosc Endosc Percutan Tech. 2024;34:619–24.
17. Kikuchi H, Endo H, Yamamoto H, Ozawa S, Miyata H, Kakeji Y, et al. Impact of reconstruction route on postoperative morbidity after esophagectomy: analysis of esophagectomies in the Japanese National Clinical Database. Ann Gastroenterol Surg. 2022;6:46–53.
18. Nakai T, Kitadani J, Ojima T, Hayata K, Katsuda M, Goda T, et al. Feeding jejunostomy following esophagectomy may increase the occurrence of postoperative small bowel obstruction. Medicine (Baltimore). 2022;101:e30746.
19. Kitagawa Y, Ishihara R, Ishikawa H, Ito Y, Oyama T, Oyama T, et al. Esophageal cancer practice guidelines 2022 edited by the Japan esophageal society: part 1. Esophagus. 2023;20:343–72.
20. Kelly RJ, Ajani JA, Kuzdzal J, Zander T, Van Cutsem E, Piessen G, et al. Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer. N Engl J Med. 2021;384:1191–203.

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