Review Article

Early detection of complications: anastomotic leakage

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Abstract: Anastomotic leakage (AL) is one of the most critical and detrimental complications in esophageal surgery. Early diagnosis and timely therapeutic action are necessary if patients are to avoid AL-related problems. However, there is no gold standard or consensus for early diagnosis. In this review, we focus on summarizing the definition and types of AL and modalities for early diagnosis of AL after esophagectomy.

Keywords: Esophageal cancer; anastomosis leakage; early diagnosis

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Introduction

The incidence of esophageal cancer is increasing globally (1). The main modality of treatment, esophagectomy, shows high morbidity and mortality rates despite advances in modern surgical techniques such as a minimally invasive surgery (2-4). Anastomotic leakage (AL) is one of the most critical and detrimental complications in esophageal surgery (2,3). The incidence of AL is about 10%, is often unpredictable in nature, and varies widely among institutions and surgeons, with a significantly higher incidence of cervical AL of 10% to 20% compared with intrathoracic AL (5-8). Given the high incidence and morbidity of AL, identification of the causes and precipitating factors, techniques for prevention, early diagnosis, and management strategies is critical (9-12). AL results in high mortality, requires repetitive therapeutic intervention and prolonged hospitalization, and is associated with poor oncological consequences from the interruptions or delays in adjuvant treatment (2,4,6,13). Early diagnosis and timely therapeutic action are necessary if patients are to avoid AL-related problems (14). However, early diagnosis and recognition of AL are difficult due to the various clinical presentations, which are often indistinguishable from the symptoms caused by physiological inflammatory response, infection, and especially pneumonia after esophagectomy (9,15). In addition, these signs and symptoms may vary from clinically silent to severely septic (11). AL usually occurs within 10 days after esophagectomy, but in some cases, it may show development as late as a few postoperative weeks (11,16). Clinical assessment alone is generally considered inadequate in early diagnosis or detection (9). Therefore, multiple methods including clinical assessments, image examinations, laboratory biomarkers, and endoscopic examinations have been proposed for early diagnosis of AL (8,9). However, there is no gold standard or consensus for early diagnosis (17,18). In this review, we focus on summarizing the definition and types of AL and modalities for early diagnosis of AL after esophagectomy.

Definitions, classifications, and risk factors

Many studies have researched AL in hopes of preventing and performing timely therapeutic intervention (8,9,14).

To discuss AL, a standardized definition and descriptions of AL are helpful (19). The Esophagectomy Complications Consensus Group has defined AL as full-thickness defects involving the esophagus, anastomosis, staple line or conduit, irrespective of the presentation or method of identification (6,20,21). For adequate management, AL is classified according to time onset, management strategy, and severity of AL (6,21,22). It can be divided into three categories according to time of onset, with dividing points at the second and seventh days after esophagectomy (22). Management of AL differs also according to time of onset; AL that develops within the first two postoperative days is likely resulted from either a technical problem or a conduit ischemia (22). This condition requires early reoperation before onset of sepsis (22). AL is also classified into three types based on treatment strategy (6,20,23). Type 1 AL is a local defect demanding no change in treatment and is treated medically or with dietary modification. Type 2 AL is also a localized defect demanding radiologic or endoscopic intervention (interventional radiology drain, stent, etc.) but not surgical therapy. Type 3 AL is a defect requiring surgical re-intervention. In addition, AL can be divided into four grades according to severity of symptoms (21,24). Grade 1 (no clinical) is diagnosed radiologically or endoscopically. Grade 2 (minor clinical) shows a local inflammatory lesion. Grade 3 (major clinical) shows severe disruption with sepsis. Grade 4 (conduit necrosis) is diagnosed by endoscopy. The following points should be considered when diagnosing AL because diagnosis and treatment of AL differ based on the variety of the disease (21,22,25). First, AL should be confirmed and classified simultaneously (21,22). Second, there is a significant difference between diagnosing suspected AL, for which the more effective tests are necessary for accuracy, and diagnosing an unsuspected case, for which the usefulness of routine tests should be assessed (21,22,24).

Understanding risk factors is an essential premise for early diagnosis of AL (26,27). High-risk cases need a more proactive approach for early diagnosis (26). Many previous studies have proposed risk factors for AL (11,14,27-30). Three types of risk factors affect development: (I) general factors, such as severe malnutrition, hemodynamic instability, chronic renal disease, coronary and vascular disease, steroid intake, diabetes mellitus, smoking history, and neoadjuvant therapy; (II) local factors, such as arterial and venous flow insufficiency, conduit problems, infection; and (III) technical factors, including anastomotic tension, location, and technique.

Early recognition and diagnosis

AL is diagnosed by either postoperative demonstration of saliva and bile via the cervical wound, or visualization of anastomotic disruption or fistula during endoscopy or re-operation (11). Initial diagnosis of AL depends on surgeon clinical experience and patient clinical manifestations, such as increased drain volume, odor, and turbidity (11,21,31). However, clinical presentations of AL can be various and range from silent to fulminant sepsis (11,14,32,33). A clinical assessment alone is inadequate for early recognition or detection (9,21). Various modalities to diagnose AL have been proposed, but a gold standard has not been established (17,18,21). Furthermore, early diagnosis of AL is very difficult, particularly in case of silent AL (9,15). Therefore, diagnosis should be early and multidisciplinary (11,14,33). Currently, early diagnosis and advanced non-surgical therapy have led to a paradigm shift in the treatment of AL, from aggressive surgical intervention to non-surgical management (3,7,33,34). Because the mortality rate of re-operations is up to 60%, most surgeons prefer non-surgical treatment (31). Surgical re-intervention should be performed only in the event of life-threatening conditions, such as conduit necrosis, diffuse peritonitis or pleurisy, and failure of non-surgical treatment (33). The need is emphasized for the introduction of novel, non-invasive tests, with high accuracy for diagnosing AL during early postoperative days (35,36). Many studies have proposed early diagnosis using clinical assessment, examination of drain fluid, and laboratory tests, endoscopy, image study, contrast esophagogram, and others. Each option is summarized below.

Clinical assessment and drain analysis

Clinical presentation of AL can be divided into nonspecific and specific cases (31,37). Nonspecific issues include tachycardia, arrhythmia, unexplained leukocytosis and respiratory failure, which are indistinguishable from other conditions such as pneumonia and infection (9,15,31,37). Signs of sepsis resulted from mediastinitis or pneumonia, are occasionally associated with arrhythmia, subcutaneous emphysema, chest pain, pneumothorax, or pleural effusion (12,31). In addition, specific issues include redness and swelling in the associated neck and chest incisions, and a change in drain nature (31). Clinical presentations of AL can be various and AL is usually initially clinically silent (11,14,33). Changes in cardiac rhythm, frequently

in the form of atrial fibrillation, can be the first and only indicator of AL (11). Therefore, clinical assessment alone is inadequate for early diagnosis or detection (9,21,38). Early diagnosis, before clinical presentation is overt, offers the best opportunity for improved prognosis and reduced sequelae (14). An early diagnosis is made mainly based on abnormal digestive fluid or pus in the drains (22,24,39). In cases of cervical AL, development of redness and swelling along the cervical wound may indicate an underlying AL (11,12). The drainage of bile, enteric content, saliva, or air via a surgically positioned drain adjacent to the anastomosis indicates a possible AL (12,14,24). With early diagnosis and treatment of AL, a tube adjacent to the anastomotic stoma can be placed at the time of surgery (22,25,39). The methylene blue swallow test is a simple and convenient method of identification—immediate discoloration of the drain will be observed after swallowing methylene blue—and is usually used for bedside diagnosis (22,31). It can prove the existence of anastomotic leaks but not determine the location or size of AL. However, this may not be proper for diagnosing late AL, as adhesions formed after esophagectomy may result in localized collection of the dye and make it difficult to identify AL (40). Recently, a mediastinal microdialysis has been reported as one of possible tools for an early diagnosis of AL (36). These clinical presentations should motivate further diagnostic studies.

Laboratory markers and findings

AL often initially presents with postoperative fever or leukocytosis (12). In addition to clinical signs, several diagnostic methods are available to help determine whether AL will develop (12). Unexplained fever or leukocytosis and erythema or induration along a cervical wound may suggest an underlying AL, and confirmatory studies for positive diagnosis will be needed (11,12). Unexplained high levels of inflammation markers (white blood cells, C-reactive protein, and lactate) in the blood may also indicate AL (8,37,41). These markers can alert surgeons to AL on the third or fourth postoperative day (9,42). Saliva or bile in a drain are also overt presentations of AL, but the level of drain amylase on the fourth postoperative day may also indicate AL earlier, a test that is reportedly more reliable than contrast esophagogram (15,20,43). In addition, recent studies have showed significant numerical correlations between AL and levels of C-reactive protein, white cell count, and albumin measured on the fourth postoperative day (10). The use of postoperative laboratory findings to predict AL is inherently difficult (and possibly not very useful) as elevated acute-phase reactant tend to be more diagnostic rather than predictive (8,9). When AL is suspected by clinical presentation and laboratory findings, both endoscopic examination and CT scan should be considered (16,17). Recently, an analysis using oral and gastric microbiome has shown that variance in the preoperative oral and gastric flora is increased when AL develops (1). Other biochemical predictor such as urinary volatile organic compounds, which reflect the metabolic status and associated with a systemic immunological response in an individual, has been reported as a possible tool for early identification of AL (35).

Endoscopy

As reported in the literatures, the first four days after esophagectomy is an exudative phase, anastomosis is unstable, and completion of mucosal resurfacing takes at least seven days (31). Most surgeons are reluctant to conduct endoscopy because of the theoretical risk of injury to the anastomosis or worsening AL (18). However, endoscopy performed within one week, even on the first operative day, after esophagectomy is safe and feasible because intraluminal pressure greater than 80 cmH_2O is known to be required to disrupt the anastomosis, while the intraluminal maximum insufflation at the anastomosis never exceeds 9 cmH_2O and rarely disturbs blood flow in the conduit (21,31,38,44-46). In addition, the procedure can be conducted at bedside, even in a patient who is on ventilation without worsening an already existing AL (12,45). The diagnostic accuracy of endoscopy is relatively high not only for evaluating the anastomosis, but also identifying the change of the integrity of the conduit, and for providing information on the vitality of the gastric conduit (21,34,43). It is also helpful in making decisions on management strategies (21,34,43). However, an endoscopic examination must be conducted with low insufflation pressure by an experienced gastroenterologist or surgeon to ovoid worsening AL (21,38). Routine examination in patients without clinical suspicion of cervical AL is controversial, because endoscopic examination with sedation may result in aspiration, and it is still not recommended as a routine method of identifying AL postoperatively (21,24,32,38). Endoscopy after esophagectomy may be necessary in cases in which the results of CT-scan are not confirmatory (16,17). In summary, endoscopy offers the advantages of possible repetitive examinations, early diagnosis, guiding further

treatments, shortening natural healing time, and reducing complications (21,31,44). Recently, fluorescence endoscopy using matrix metalloproteinase, which plays a crucial role in regulation of wound healing, have been reported as a promising tool for early identification of AL in a murine model (47).

Contrast esophagogram

Esophagectomy can lead to impaired swallowing function, and esophagogram should be performed in with great care, especially in case of impaired consciousness, because of the risk of aspiration (17,24,43). Contrast esophagogram involves a water-soluble contrast agent to prevent aggravation of sepsis by the barium leakage, followed by barium administration to improve the diagnosis accuracy for diagnosing AL (12,22,43). However, even a negative esophagogram finding does not exclude AL because of a false-negative rate of 57%, especially in cervical anastomosis (5,48). Consequently, this method is regarded as a questionable diagnostic modality to diagnose AL (5). Some studies have reported that patients without signs or symptoms suggestive of AL do not benefit from a contrast esophagogram (24,32). However, contrast esophagogram can provide information on the integrity and passage disturbance of the esophagus, a conduit, and a pyloroplasty (5,21). The examination is most commonly performed on the fifth to seventh postoperative days, which is usually considered too late for early diagnosis (32).

Image study

Even normal radiographic results on the seventh postoperative day do not exclude the occurrence of a life-threatening AL a few days later (14). The first sign of AL is a pleural effusion or infiltration on chest radiography (14). The occurrence of a new pleural effusion, especially adjacent to an intrathoracic anastomosis, within the first days after esophagectomy should be considered evidence of AL until other causes such as chylothorax are ruled out (12,14). CT scan provides visualization of the neck, thorax, and abdomen on one single examination (12,21). It allows not only identification of an AL, but also helps determine the degree and location of extra-luminal fluid collections demanding drainage and can diagnose conditions such as pneumonia (12,24). Sensitivity of CT scan in identifying fistula, wall discontinuity, and mediastinal fluid or air approaches 80% (21). However, interpretation of CT scan findings immediately after esophagectomy is challenging due to the anatomic changes and those of residual fluid and air and a lack of consensus on CT scan findings associated with AL (12,18,21). Standardization of CT findings has been suggested to overcome these limitations (18,21). Fistula, mediastinal fluid and air collection, and esophagogastric wall discontinuity are reported to be independently associated with AL, irrespective of clinical and treatment-related patient characteristics (18,21). This allows early diagnosis and leads to a reduction in treatment delays during other tests (49). If the CT scan findings are uncertain, endoscopy should be performed immediately, as this has been considered accurate and safe for diagnosis of AL (11). Recently, a CT-based score provided better diagnostic performance for diagnosis of AL (18). CT scanning is usually conducted for detecting postoperative complications, as it is non-invasive and safe to perform in critically ill patients, irrespective of time and help to detect other associated findings (18,33). Recently, positron emission tomography-CT has been reported to be a possible tool for early detecting ischemia of the gastric conduit in a rat model (50).

Conclusions

A gold standard for diagnosing AL, aside from early diagnosis, has not yet been established. Early diagnosis, while the cornerstone of a timely therapeutic approach to avoiding AL-related problems, has proven extremely challenging. Multidisciplinary approaches including identification of risk factors, clinical assessments, laboratory findings, endoscopy, and imaging techniques can help surgeons to establish an accurate and timely diagnosis of AL. Currently, early diagnosis and advanced non-surgical therapy are driving a paradigm shift in the management of AL from aggressive surgical re-intervention to non-surgical management. Further studies should be performed to establish a consensus on optimal approaches for early diagnosis of AL.

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Footnote

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References

1. Reddy RM, Weir WB, Barnett S, et al. Increased Variance in Oral and Gastric Microbiome Correlates With Esophagectomy Anastomotic Leak. Ann Thorac Surg 2018;105:865-70.
2. van Rossum PS, Haverkamp L, Carvello M, et al. Management and outcome of cervical versus intrathoracic manifestation of cervical anastomotic leakage after transthoracic esophagectomy for cancer. Dis Esophagus 2017;30:1-8.
3. Hu Z, Yin R, Fan X, et al. Treatment of intrathoracic anastomotic leak by nose fistula tube drainage after esophagectomy for cancer. Dis Esophagus 2011;24:100-7.
4. Rutegård M, Lagergren P, Rouvelas I, et al. Intrathoracic anastomotic leakage and mortality after esophageal cancer resection: a population-based study. Ann Surg Oncol 2012;19:99-103.
5. Jones CM, Clarke B, Heah R, et al. Should routine assessment of anastomotic integrity be undertaken using radiological contrast swallow after oesophagectomy with intra-thoracic anastomosis? Best evidence topic (BET). Int J Surg 2015;20:158-62.
6. Schlottmann F, Molena D. Anastomotic leak: an early complication with potentially long-term consequences. J Thorac Dis 2016;8:E1219-20.
7. Ma H, Wang J, Xi Q, et al. Analysis of Endoscopy Intervention in Postesophagectomy Anastomotic Leak: A Retrospective Study. Thorac Cardiovasc Surg 2018. [Epub ahead of print].
8. Findlay JM, Tilson RC, Harikrishnan A, et al. Attempted validation of the NUn score and inflammatory markers as predictors of esophageal anastomotic leak and major complications. Dis Esophagus 2015;28:626-33.
9. Park JK, Kim JJ, Moon SW. C-reactive protein for the early prediction of anastomotic leak after esophagectomy in both neoadjuvant and non-neoadjuvant therapy case: a propensity score matching analysis. J Thorac Dis 2017;9:3693-702.
10. Noble F, Curtis N, Harris S, et al. Risk assessment using a novel score to predict anastomotic leak and major complications after oesophageal resection. J Gastrointest Surg 2012;16:1083-95.
11. Messager M, Warlaumont M, Renaud F, et al. Recent improvements in the management of esophageal anastomotic leak after surgery for cancer. Eur J Surg Oncol 2017;43:258-69.
12. Jones CE, Watson TJ. Anastomotic Leakage Following Esophagectomy. Thorac Surg Clin 2015;25:449-59.
13. Markar S, Gronnier C, Duhamel A, 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.
14. Paul S, Bueno R. Section VI: complications following esophagectomy: early detection, treatment, and prevention. Semin Thorac Cardiovasc Surg 2003;15:210-5.
15. Berkelmans GH, Kouwenhoven EA, Smeets BJ, et al. Diagnostic value of drain amylase for detecting intrathoracic leakage after esophagectomy. World J Gastroenterol 2015;21:9118-25.
16. Struecker B, Andreou A, Chopra S, et al. Evaluation of Anastomotic Leak after Esophagectomy for Esophageal Cancer: Typical Time Point of Occurrence, Mode of Diagnosis, Value of Routine Radiocontrast Agent Studies and Therapeutic Options. Dig Surg 2018;35:419-26.
17. Strauss C, Mal F, Perniceni T, et al. Computed tomography versus water-soluble contrast swallow in the detection of intrathoracic anastomotic leak complicating esophagogastrectomy (Ivor Lewis): a prospective study in 97 patients. Ann Surg 2010;251:647-51.
18. Goense L, Stassen PMC, Wessels FJ, et al. Diagnostic performance of a CT-based scoring system for diagnosis of anastomotic leakage after esophagectomy: comparison with subjective CT assessment. Eur Radiol 2017;27:4426-34.
19. Chen KN. Managing complications I: leaks, strictures, emptying, reflux, chylothorax. J Thorac Dis 2014;6 Suppl 3:S355-63.
20. Jiang B, Ho VP, Ginsberg J, et al. Decision analysis supports the use of drain amylase-based enhanced recovery method after esophagectomy. Dis Esophagus 2018;31:doy041.
21. Grimminger PP, Goense L, Gockel I, et al. Diagnosis, assessment, and management of surgical complications following esophagectomy. Ann N Y Acad Sci 2018;1434:254-73.
22. Tang H, Xue L, Hong J, et al. A method for early diagnosis and treatment of intrathoracic esophageal anastomotic leakage: prophylactic placement of a drainage tube adjacent to the anastomosis. J Gastrointest Surg 2012;16:722-7.
23. Freeman RK, Ascioti AJ, Dake M, et al. An Assessment of the Optimal Time for Removal of Esophageal Stents Used in the Treatment of an Esophageal Anastomotic Leak or Perforation. Ann Thorac Surg 2015;100:422-8.

24. Nederlof N, de Jonge J, de Vringer T, et al. Does Routine Endoscopy or Contrast Swallow Study After Esophagectomy and Gastric Tube Reconstruction Change Patient Management? J Gastrointest Surg 2017;21:251-8.
25. Ding N, Mao Y, He J, et al. Experiences in the management of anastomotic leakages and analysis of the factors affecting leakage healing in patients with esophagogastric junction cancer. J Thorac Dis 2017;9:386-91.
26. Wright CD, Kucharczuk JC, O'Brien SM, et al. Predictors of major morbidity and mortality after esophagectomy for esophageal cancer: a Society of Thoracic Surgeons General Thoracic Surgery Database risk adjustment model. J Thorac Cardiovasc Surg 2009;137:587-95; discussion 596.
27. Kassis ES, Kosinski AS, Ross P Jr, et al. Predictors of anastomotic leak after esophagectomy: an analysis of the society of thoracic surgeons general thoracic database. Ann Thorac Surg 2013;96:1919-26.
28. Reavis KM. The esophageal anastomosis: how improving blood supply affects leak rate. J Gastrointest Surg 2009;13:1558-60.
29. Okamura A, Watanabe M, Imamura Y, et al. Preoperative Glycosylated Hemoglobin Levels Predict Anastomotic Leak After Esophagectomy with Cervical Esophagogastric Anastomosis. World J Surg 2017;41:200-7.
30. Mier F, Oelschlager BK. Prevention of leaks in esophageal surgery. J Gastrointest Surg 2011;15:1316-8.
31. Low DE. Diagnosis and management of anastomotic leaks after esophagectomy. J Gastrointest Surg 2011;15:1319-22.
32. Solomon DG, Sasaki CT, Salem RR. An evaluation of the routine use of contrast radiography as a screening test for cervical anastomotic integrity after esophagectomy. Am J Surg 2012;203:467-71.
33. Girard E, Messager M, Sauvanet A, et al. Anastomotic leakage after gastrointestinal surgery: diagnosis and management. J Visc Surg 2014;151:441-50.
34. Licht E, Markowitz AJ, Bains MS, et al. Endoscopic Management of Esophageal Anastomotic Leaks After Surgery for Malignant Disease. Ann Thorac Surg 2016;101:301-4.
35. Plat VD, van Gaal N, Covington JA, et al. Non-Invasive Detection of Anastomotic Leakage Following Esophageal and Pancreatic Surgery by Urinary Analysis. Dig Surg 2019;36:173-80.
36. Ellebæk M, Qvist N, Fristrup C, et al. Mediastinal microdialysis in the diagnosis of early anastomotic leakage after resection for cancer of the esophagus and gastroesophageal junction. Am J Surg 2014;208:397-405.
37. Tsujimoto H, Ono S, Takahata R, et al. Systemic inflammatory response syndrome as a predictor of anastomotic leakage after esophagectomy. Surg Today 2012;42:141-6.
38. Page RD, Asmat A, McShane J, et al. Routine endoscopy to detect anastomotic leakage after esophagectomy. Ann Thorac Surg 2013;95:292-8.
39. Schaheen L, Blackmon SH, Nason KS. Optimal approach to the management of intrathoracic esophageal leak following esophagectomy: a systematic review. Am J Surg 2014;208:536-43.
40. Kapila S, Rozen WM, Huang T, et al. Determining between chyle leak and anastomotic leak after esophageal reconstruction: the utility of methylene blue dye. Laryngoscope 2012;122:779-80.
41. Ip B, Ng KT, Packer S, et al. High serum lactate as an adjunct in the early prediction of anastomotic leak following oesophagectomy. Int J Surg 2017;46:7-10.
42. Asti E, Bonitta G, Melloni M, et al. Utility of C-reactive protein as predictive biomarker of anastomotic leak after minimally invasive esophagectomy. Langenbecks Arch Surg 2018;403:235-44.
43. Miller DL, Helms GA, Mayfield WR. Evaluation of Esophageal Anastomotic Integrity With Serial Pleural Amylase Levels. Ann Thorac Surg 2018;105:200-6.
44. Lin TH, Huang PM. Early Postoperative Endoscopy for Evaluation of the Anastomosis after Esophageal Reconstruction. Thorac Cardiovasc Surg 2018;66:376-83.
45. Nishikawa K, Fujita T, Yuda M, et al. Early postoperative endoscopy for targeted management of patients at risks of anastomotic complications after esophagectomy. Surgery 2016;160:1294-301.
46. Fujiwara H, Nakajima Y, Kawada K, et al. Endoscopic assessment 1 day after esophagectomy for predicting cervical esophagogastric anastomosis-relating complications. Surg Endosc 2016;30:1564-71.
47. Neumann PA, Twardy V, Becker F, et al. Assessment of MMP-2/-9 expression by fluorescence endoscopy for evaluation of anastomotic healing in a murine model of anastomotic leakage. PLoS One 2018;13:e0194249.
48. Roh S, Iannettoni MD, Keech JC, et al. Role of Barium Swallow in Diagnosing Clinically Significant Anastomotic Leak following Esophagectomy. Korean J Thorac Cardiovasc Surg 2016;49:99-106.
49. Kanaji S, Ohyama M, Yasuda T, et al. Can the

intraoperative leak test prevent postoperative leakage of esophagojejunal anastomosis after total gastrectomy? Surg Today 2016;46:815-20.
50. Park SY, Kang WJ, Cho A, et al. 64Cu-ATSM Hypoxia Positron Emission Tomography for Detection of Conduit Ischemia in an Experimental Rat Esophagectomy Model. PLoS One 2015;10:e0131083.

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