



The 33-year Retrospective Analysis of Esophageal Carcinomas: Cerrahpaşa Experience

Özefagus Karsinomlarının 33 Yıllık Retrospektif Analizi: Cerrahpaşa Deneyimi

Server Sezgin ULUDAĞ¹, Ozan AKINCI², Sefa ERGÜN¹, Ergin ERGİNÖZ¹, Ahmet Necati ŞANLI¹, Nuray KEPİL³,
Fadıl AYAN¹, Mehmet Faik ÖZÇELİK¹, Abdullah Kağan ZENGİN¹

¹*Istanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of General Surgery, İstanbul, Turkey*

²*Kartal Dr. Lütfi Kırdar City Hospital, Clinic of General Surgery, İstanbul, Turkey*

³*Istanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Pathology, İstanbul, Turkey*

ABSTRACT

Aim: Esophageal cancer is a fatal disease where the majority of patients are diagnosed at an advanced stage. In this study, we aimed to present the demographic and clinicopathological characteristics of patients who were operated for esophageal cancer.

Materials and Methods: A total of 847 patients who underwent surgery, chemoradiotherapy, or palliative procedures for esophageal pathology between the years of 1985 and 2018 were retrospectively analyzed. Age, gender, tumor location, histopathology, surgical technique, and chemoradiotherapy history of patients were analyzed.

Results: In the study, 488 patients were male (60.5%) and 319 were female (39.5%). The ratio of males and females was 1.52. The average age was 58.6 years, and 80.1% were older than 50 years. The most common pathological material obtained was squamous cell carcinoma (67.5%), followed by adenocarcinoma (27.7%). Total esophagectomy was performed in 435 patients; distal esophagectomy was performed in 38 patients. Transhiatal esophagectomy (n=271, 62.2%) was the most common procedure that was performed.

Conclusion: Esophagectomy is the primary treatment modality for esophageal cancers. When determining the optimal treatment, appropriate patient selection, staging, and risk assessment should be made. Patient-specific treatment should be planned with a multidisciplinary approach.

Keywords: Esophageal cancer, Cerrahpaşa, esophagus, carcinoma

ÖZ

Amaç: Özefagus kanseri, hastaların çoğunun ileri evrede teşhis edildiği ölümcül bir hastalıktır. Bu çalışmada özefagus kanseri nedeniyle ameliyat edilen hastaların demografik ve klinikopatolojik özelliklerini sunmayı amaçladık.

Gereç ve Yöntem: 1985-2018 yılları arasında özefagus patolojisi nedeniyle cerrahi, kemoradyoterapi veya palyatif prosedürler uygulanan toplam 847 hasta retrospektif olarak incelendi. Hastaların yaş, cinsiyet, tümör yerleşimi, histopatolojisi, cerrahi teknik ve kemoradyoterapi öyküleri incelendi.

Bulgular: Çalışmada 488 hasta erkek (%60,5) ve 319 hasta kadındı (%39,5). Katılımcıların yaş ortalaması 58,6 olup, %80,1'i 50 yaşın üzerindedi. Erkeklerin ve kadınların oranı sırasıyla %60,5 ve %39,5 idi. Elde edilen en yaygın patoloji materyali skuamöz hücreli karsinom (%67,5), ardından adenokarsinomdu (%27,7). Toplam özefajektomi 435 hastaya yapıldı ve 38 hastaya distal özefajektomi yapıldı. Transhiatal özefajektomi (n=271, %62,2) en sık yapılan işlemdi.

Sonuç: Özefajektomi, özefagus kanserleri için birincil tedavi yöntemidir. Optimal tedaviyi belirlerken uygun hasta seçimi, evreleme ve risk değerlendirmesi yapılmalıdır. Hastaya özel tedavi multidisipliner bir yaklaşımla planlanmalıdır.

Anahtar Kelimeler: Özefagus kanseri, Cerrahpaşa, özefagus, karsinom

Address for Correspondence: Ergin Erginöz MD, İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of General Surgery, İstanbul, Turkey

Phone: +90 536 879 97 71 **E-mail:** eerginoz@ku.edu.tr **ORCID ID:** orcid.org/0000-0002-8349-3298

Received: 27.10.2020 **Accepted:** 14.01.2021

INTRODUCTION

Esophageal cancer is accepted as one of the deadliest cancers of the digestive tract. It is ranked sixth among all cancers over the world and it constitutes about 5-7% of all cancers^{1,2}. Besides its longitudinal spread, the tumor may spread from the esophageal mucosa towards the submucosa and can reach the mediastinal region as well as abdominal lymph nodes by draining through the peripheral lymph nodes via perforating lymph vessels. This drainage pathway can explain why many patients are at an advanced stage at the time when the diagnosis is made.

In countries where the disease is common, diagnosis can be made at an early stage due to the developed and different screening modalities. The esophageal cancer incidence varies widely by geographical locations. "Asian Esophageal Cancer Belt" is a region that begins from Turkey, Iraq, Iran, and Kazakhstan extending up all the way to northern China. Most of the esophageal cancers in this region are squamous cell carcinoma (SCC) and it is the region with the highest incidence of esophageal cancer in the world³. In Turkey, SCC is seen most commonly in the Eastern Anatolia Region². While SCC is the most common histological type over the world, the incidence of adenocarcinoma has gradually increased and has become dominant over time, especially in western countries⁴. The main goal of the treatment of esophageal carcinoma is to improve patient's quality of life as well as to eliminate dysphagia, which is one of the most common symptoms known. While optimistic results are obtained in early stage esophageal cancer due to the anatomical features of the esophagus, the results are poor in the advanced metastatic stage⁵. Numerous studies have reported that the substantial results are obtained through a multidisciplinary approach in the treatment of esophageal cancer⁶⁻⁹. Although the standard treatment for early esophageal carcinomas is esophagectomy, various endoscopic treatment methods have been developed for some early esophageal tumors in the past two decades. The first successful esophageal resection was performed by the French surgeon Torek in 1913¹⁰. Today, proximal, distal, and total esophagectomy is performed in many clinics using open or minimally invasive techniques. Reconstruction is successfully established with the help of stomach, colon and small intestine via flaps or free flaps. In this study, we aimed to present the demographic, clinical, and pathological characteristics of patients who were operated in our clinic for esophageal cancer.

MATERIALS AND METHODS

In this retrospective study, a total of 847 patients who underwent surgery, chemoradiotherapy, or palliative procedures for esophageal pathology in the Department of General Surgery of Cerrahpaşa Medical Faculty between 1985 and 2018 were examined. Ethics committee approval was obtained for the study. Patients older than 18 years of age, patients operated under elective conditions due to malignant lesions (adenocarcinoma and SCC) of the esophagus, patients

who underwent palliative stenting or enteral feeding tube due to inoperable state, or those who were treated with chemoradiotherapy were included in the study. Patients with benign lesions, leiomyoma and gastrointestinal (GIS) stromal tumor according to histopathological results were excluded from the study (n=40). Patients over the age of 18 years, who were operated on for trauma or other emergency indications, were excluded. The study was designed on 807 patients.

Patient data were obtained from discharge reports, surgical reports, and pathology reports in the hospital database. Age, gender, symptoms, location of the tumor, histopathological diagnosis, applied surgical technique, neoadjuvant and adjuvant radiotherapy and chemotherapy history of the patients were recorded. In addition, the clinical stages of the patients were evaluated according to the tumor node metastasis (TNM) staging system⁵. Patients with no metastases and no contraindications for the operation were considered eligible for surgical resection. Various surgical techniques are available for the surgery of the esophagus. Transhiatal esophagectomy was defined as total esophagectomy with the addition of abdominal and cervical incisions without thoracotomy. The Ivor Lewis procedure was defined as esophagectomy with abdominal and right thoracic incisions. Lastly, the McKeown's operation was defined as esophagectomy with abdominal, right thoracic and cervical incisions.

Statistical Analysis

Descriptive statistics were carried out. Mean and standard deviation was calculated for continuous variables, and frequencies and numbers for categorical variables. Inferential statistical analysis could not be performed because there was no group comparison.

RESULTS

The average age of 847 patients was 58.1 years and 521 (61.5%) were male and 326 (38.4%) were female. The mean age of the patients included in the study with esophageal malignancy (adenocarcinoma and SCC) (n=807) was 58.6 years and 80.1% of them were older than 50 years (Table 1). The rates of males and females in patients with esophageal malignancies were 60.5% and 39.5%, respectively (male/female=1.52). The average age of male patients was 59.2 (20-89) years, and the average age of female patients was 57.6 (18-86) years. In terms of symptoms, dysphagia was seen in 90%, weight loss was seen in 64%, odynophagia was seen in 15%, hematemesis was seen in 4%, and cough and hoarseness were seen in 2% of the patients.

As a result of the pathological examination of the endoscopic biopsy and surgical resection materials, it was found that 95.2% (n=807) of the cases had malignant esophageal neoplasms. In pathology materials, SCC was observed the most frequently (67.5%) and the second most common was adenocarcinoma (27.7%). The rest of the pathologies included chronic esophagitis,

GIS stromal tumors, and leiomyoma in decreasing order or observation (Table 1). In terms of tumor grade, 9.3% of the tumors were well differentiated (Grade 1), 50% were moderately differentiated (Grade 2), 18.5% were poorly differentiated (Grade 3), and 4.2% were very poorly differentiated (Grade 4). The rate of cases whose histopathological grade could not be determined (Grade X) was 17.8%. When the cases of esophagitis were examined, it was seen that these patients were operated due to corrosive substance drinking or stricture secondary to chronic esophagitis. Tumors were most commonly localized in the distal esophagus (44.9%), followed by middle and upper esophagus in decreasing order of occurrence (Table 1). Surgical resection was performed in 473 of the patients. Total esophagectomy was performed in 435 patients, and distal esophagectomy was performed in 38 patients. Transhiatal esophagectomy (n=271, 62.2%) was accepted to be the most common total esophagectomy procedure performed (Table 1). In 187 patients who were not operated due to irresectable state, neoadjuvant chemotherapy was applied. Enteral feeding tube for palliative therapy was applied to 63 patients with metastatic esophageal cancer, and esophageal stent procedure was applied

to 31 patients. In the study, 93 patients who continued their treatment in other centers or refused treatment were excluded from follow-up. GIS continuity was established by anastomosis of the stomach with the proximal esophagus inside the thorax in cases who underwent distal esophagectomy. Among the patients who underwent total esophagectomy, 374 patients were reconstructed with stomach interposition (86%), 48 patients were reconstructed with colon interposition (11%), and 13 patients were reconstructed with jejunum interposition (3%).

DISCUSSION

The incidence, morbidity, and mortality rates of esophageal cancer have varied greatly over the past 30 years, but it is still one of the cancer types with the highest mortality worldwide. In both sexes, the incidence of esophageal cancer increases proportionally with age and it peaks at the 7th decade¹¹. The incidence in men is observed to be 2-4 times higher than that in women¹². This male to female ratio rate has been reported as 4.9 in adenocarcinomas and 1.2 in SCC¹³. In our study, 58.4% of the patients with esophageal cancer were between the ages of 50 and 70 years, and the male/female ratio was 1.52. It was seen that the demographic features in this study were compatible with the literature.

In esophageal cancer, dysphagia is the most common presenting symptom, followed by weight loss⁷. Smoking, alcohol intake, poor diet, poor socioeconomic conditions, infections (such as HIV, *Helicobacter pylori*), genetic factors, gastroesophageal reflux and Barrett's esophagus are the main risk factors¹⁴. For this reason, especially in elder patients who present with dysphagia and have a history of risk factors considered to be as a red flag, esophageal imaging should be promptly completed first followed by endoscopy in order to exclude esophageal malignancy. In our series, the most common presenting symptom was dysphagia.

Esophageal cancers are mainly observed in the lower one-third segment of the esophagus, followed by the middle one-third and upper one-third segments, in decreasing order of occurrence¹⁵. While nearly 75% of all adenocarcinomas are localized to the distal esophagus, SCC are equally distributed in the distal two-thirds segment of the esophagus¹⁶. In our study, in accordance with the literature, esophageal malignancies were mostly located in the lower 1/3 segment.

Until 30 years ago, the ratio of SCC to adenocarcinoma of esophagus cancer was higher in favor of SCC. Since 2000's, this ratio seemed to increase in favor of adenocarcinoma (5:1) possibly due to the various adaptations of the risk factors^{13,17}. Although the underlying cause may change, the reason for this change in the histopathological pattern is unknown since many different risk factors are involved in the development of esophageal cancer^{7,13}. In our study, 67.5% of the patients had SCC, while 27.7% of the patients had adenocarcinoma. We believe that the reason why the rate of adenocarcinoma is not

Table 1. Demographic, pathological and surgical results of the study

Age	Female n (%)	Male n (%)	Total n (%)
<29	4	8	12 (1.48)
30-39	24	30	54 (6.69)
40-49	42	52	94 (11.64)
50-59	67	125	192 (23.79)
60-69	109	171	280 (34.69)
>70	73	102	175 (21.68)
Total	319 (39.5)	488 (60.5)	807
Histological diagnosis		n (%)	
Squamous cell carcinoma		572 (67.5)	
Adenocarcinoma		235 (27.7)	
Esophagitis*		26 (3.0)	
Leiomyoma		8 (0.9)	
GIST**		6 (0.7)	
Anatomical localization		n (%)	
Upper 1/3 esophagus		172 (21.3)	
Middle 1/3 esophagus		273 (33.8)	
Lower 1/3 esophagus		362 (44.9)	
Total		807 (100)	
Surgical technique		n (%)	
Transhiatal esophagectomy		271 (62.2)	
Ivor Lewis procedure		82 (18.8)	
McKeown procedure		57 (13.1)	
Minimally invasive (toracoscopic + laparoscopic)		25 (5.7)	
Total		435 (100)	
*Chronic esophagitis and esophagitis secondary to corrosive damage.			
**Gastrointestinal stromal tumor.			
GIST: Gastrointestinal stromal tumors			

as dominant as reported in the literature is that our country is in the Asian Esophageal Cancer Belt and SCC is the dominant type like other societies in this generation.

The TNM classification system is widely used for the staging of esophageal cancer. Staging is a key factor in determining the method of treatment. Although the most important radiological imaging in staging is ^{18}F -fluoro-2-deoxy-D-glucose positron emission tomography and endoscopic ultrasonography, laparoscopy and/or thoracoscopy also has an important role in selected cases¹⁸.

The ideal treatment method for esophageal cancer has not been determined. Multimodal therapies using chemotherapy or chemoradiotherapy combined with surgical treatment give promising results. Treatment is adjusted according to the stage of the disease and clinical evaluation of the patient. Curative and palliative surgery, endoscopic intervention, medical oncology, and radiotherapy treatments are tailored for each patient. Endoscopic mucosal resection (EMR) is a reliable and curative treatment for early esophageal cancers (Tis and T1a, T1b_{sm1})¹⁹. However, we did not have EMR experience in our clinic. Esophagectomy is the preferred treatment for T1b, submucosal layer-1 (s1), s2, and s3 tumors with lymphovascular invasion or other risk factors⁹. Neoadjuvant chemoradiotherapy and esophagectomy (with lymphadenectomy) should be performed in locally advanced resectable tumors. Chemotherapy, chemoradiotherapy and palliative treatments are reserved for non-resectable tumors. Salvage esophagectomy is the surgical method of choice for residual tumor or recurrence after chemoradiotherapy⁹.

Currently, the most common open operations in resectable cases are transhiatal esophagectomy, Ivor Lewis surgery, and McKeown surgery^{7,20}. Wide resection should be performed in these operations since esophageal tumors can spread submucosally throughout the esophageal layers and SCC causes longitudinal lymph flow skipping areas²¹. Hagen et al.²² reported that survival was significantly better in the patient group who underwent en-block esophagectomy compared to the transhiatal esophagectomy group. In contrast, in a randomized clinical study by Hulscher et al.²³ in which transhiatal lymphadenectomy in 106 patients and transthoracic plus en-block lymphadenectomy in 114 patients was performed, it was observed that there was no difference between these two techniques in terms of postoperative mortality, but the complication rate of transthoracic resection and length of hospital stay were seen to be higher. In transhiatal esophagectomy, blind esophagectomy is performed without thoracotomy; although the failure of intrathoracic lymphadenectomy is the weakest aspect of the method, the complication rate, especially pulmonary complications, is observed less than surgeries that involve thoracotomy. This is also the type of operation that patients are able to tolerate better. In the last 33 years, we found that transhiatal esophagectomy technique was the most preferred technique (62.2%) in our

clinic. One of the most important criteria in the selection of surgical technique is the surgeon's experience. For this reason, the surgeons in our clinic did not prefer the mediastinal anastomosis, so total esophagectomy was the most performed. In our clinic, mostly stomach was used for reconstruction. However, as is known, it can be performed in jejunum and colon interposition. Colon and jejunum reconstructions require more anastomosis than stomach reconstructions, technically more difficult and septic complications may occur. Therefore, it was not preferred in our clinic except for recurrence cases.

Advantages of minimally invasive esophagectomy, which has been increasingly applied in the last two decades, include smaller incisions, preservation of post-operative pulmonary function, fewer blood loss and complications, and shorter intensive care and hospital stay²⁴⁻²⁶. There are publications on the long-term oncological results of minimally invasive surgeries and whether the surgical margins of the esophagus and stomach are sufficient. However, in recent randomized controlled prospective studies, minimally invasive surgery was found to be noninferior in terms of oncologic results compared to open esophagectomy^{27,28}. Minimally invasive surgery is used safely for oncological pathologies as well as benign pathologies (diverticulectomy)²⁹. Thoracoscopic and laparoscopic total esophagectomy has been successfully performed in 25 cases in our clinic.

T4b tumors are the advanced stage cancers that invade non-resectable structures such as the aorta, left atrium, and spine. In these cases where curative treatment is not possible, palliative modalities should be performed towards symptoms in order to delay death. Chemoradiotherapy is a preferred approach for patients who are eligible for combined therapy because it provides better palliation than radiotherapy alone and increases the probability of long-term progression-free survival³⁰. Patients who can take semi-solid food are treated with chemoradiotherapy, and radiotherapy is effective after six weeks³¹. Palliation can be established with an endoscopic stent in patients who can only take fluid or cannot swallow saliva. Endoscopic dilatation is another technique of treatment modality performed in these patients. Percutaneous endoscopic gastrostomy, tube gastrostomy/ jejunostomy can be applied for nutritional support in patients who are not suitable for stenting or dilatation³².

Study Limitations

Since our study is a retrospective clinical study, data regarding disease stage, intraoperative and postoperative complications, mortality rates and survival times of many patients could not be obtained. In addition, the fact that it is single-centered institutional study and the fact that the treatment modalities have been updated in 33 years are the other limitations of our study.

CONCLUSION

Esophagectomy is still the main treatment method for esophageal cancers, but the majority of patients are

unresectable due to systemic spread at the time of diagnosis. We believe that through better follow-up and surveillance programs, aggressive multidisciplinary approach, and development of minimally invasive methods, morbidity of esophagectomy will decrease, survival will be prolonged, and patients' quality of life will increase.

Ethics

Ethics Committee Approval: The study were approved by the İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine (date: 09.07.2020, protocol number: 86672).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.S.U., F.A., M.F.Ö., A.K.Z., Concept: S.S.U., O.A., S.E., F.A., M.F.Ö., A.K.Z., Design: S.S.U., O.A., S.E., F.A., M.F.Ö., A.K.Z., Data Collection or Processing: S.S.U., O.A., S.E., E.E., A.N.Ş., N.K., Analysis or Interpretation: S.S.U., O.A., S.E., E.E., A.N.Ş., N.K., Literature Search: S.S.U., O.A., S.E., E.E., A.N.Ş., N.K., Writing: S.S.U., O.A., S.E., E.E., A.N.Ş.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

- Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin*. 2015;65:5-29.
- Okten I. "Özofagus Kanseri." Ankara: İstanbul Tıp Kitabevi; 2003.p.1247-308.
- Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. *J Clin Oncol*. 2006;24:2137-50.
- Cook MB, Chow WH, Devesa SS. Esophageal cancer incidence in the United States by race, sex, and histologic type, 1977-2005. *Br J Cancer*. 2009;101:855-9.
- Rice TW, Kelsen D, Blackstone EH, Ishwaran H, Patil DT, Bass AJ, et al. Esophagus and Esophagogastric Junction. *AJCC Cancer Staging Manual*. 2017;185-202.
- Pennathur A, Luketich JD. Resection for esophageal cancer: strategies for optimal management. *Ann Thorac Surg*. 2008;85:751-6.
- Pennathur A, Gibson MK, Jobe BA, Luketich JD. Esophageal carcinoma. *Lancet*. 2013;381:400-12.
- Polednak AP. Trends in survival for both histologic types of esophageal cancer in US surveillance, epidemiology and end results areas. *Int J Cancer*. 2003;105:98-100.
- Jobe BA, Landreneau RJ, Habib F. "The Management of Esophageal Cancer." Cameron JL, Cameron. AM, editors. *Current Surgical Therapy*. 12th edition. Elsevier; 2017. p. 53-62. Available from: <https://www.elsevier.com/books/current-surgical-therapy/cameron/978-0-323-46117-7>
- Fujita H. Anesthesia of Torek's operation: the first successful resection of a cancer in the thoracic esophagus-an abridged translation of an essay in Japanese. *Gen Thorac Cardiovasc Surg*. 2017;65:80-4. Epub 2016 Dec 29.
- Howlander N, Noone AM, Krapcho M, Neyman N, Aminou R, Waldron W, Altekruse SF, Kosary CL, Ruhl J, Tatalovich Z, Cho H, Mariotto A, Eisner MP, Lewis DR, Chen HS, Feuer EJ, Cronin KA, Edwards BK (eds). *SEER Cancer Statistics Review, 1975-2008*, National Cancer Institute. Bethesda, MD. Available from: https://seer.cancer.gov/csr/1975_2008/
- Zhang Y. Epidemiology of esophageal cancer. *World J Gastroenterol*. 2013;19:5598-606.
- Schlansky B, Dimarino Jr AJ, Loren D, Infantolino A, Kowalski T, Cohen S. "A Survey of Esophageal Cancer: Pathology, Stage and Clinical Presentation." *Aliment Pharmacol Ther*. 2006;23:587-93.
- Asombang AW, Chishinga N, Nkhoma A, Chipaila J, Nsokolo B, Manda-Mapalo M, et al. Systematic review and meta-analysis of esophageal cancer in Africa: Epidemiology, risk factors, management and outcomes. *World J Gastroenterol*. 2019;25:4512-33.
- Berry MF. Esophageal cancer: staging system and guidelines for staging and treatment. *J Thorac Dis*. 2014;3:289-97.
- Enzinger PC, Mayer RJ. Esophageal cancer. *N Engl J Med*. 2003;349:2241-52.
- Pohl H, Sirovich B, Welch HG. Esophageal adenocarcinoma incidence: are we reaching the peak? *Cancer Epidemiol Biomarkers Prev*. 2010;19:1468-70.
- Espat NJ, Jacobsen G, Horgan S, Donahue P. Minimally invasive treatment of esophageal cancer: laparoscopic staging to robotic esophagectomy. *Cancer J*. 2005;11:10-7.
- Ishihara R, Tanaka H, Iishi H, Takeuchi Y, Higashino K, Uedo N, et al. Long-term outcome of esophageal mucosal squamous cell carcinoma without lymphovascular involvement after endoscopic resection. *Cancer*. 2008;112:2166-72.
- Ajani JA, D'amico TA, Bentrim DJ, Chao J, Corvera C, Das P, et al. "Esophageal and Esophagogastric Junction Cancer" Version 2.2019. *NCCN Clinical Practice Guidelines in Oncology*. 2019;17:855-83.
- Ozcelik MF. Özofagus Kanseri: Tanı ve Cerrahi Tedavi. *Gastrointestinal Sistem Hastalıkları*. İstanbul, İ.Ü. Cerrahpaşa Tıp Fakültesi; 2001. p. 241-51.
- Hagen JA, Peters JH, DeMeester TR. Superiority of extended en bloc esophagogastrectomy for carcinoma of the lower esophagus and cardia. *J Thorac Cardiovasc Surg*. 1993;106:850-8.
- Hulscher JB, Tijssen JG, Obertop H, van Lanschot JJ. Transthoracic versus transhiatal resection for carcinoma of the esophagus: a meta-analysis. *Ann Thorac Surg*. 2001;72:306-13.
- Levy RM, Pennathur A, Luketich JD. Randomized trial comparing minimally invasive esophagectomy and open esophagectomy: early perioperative outcomes appear improved with a minimally invasive approach. *Semin Thorac Cardiovasc Surg*. 2012;24:153-4.
- Luketich JD, Pennathur A, Awais O, Levy RM, Keeley S, Shende M, et al. Outcomes after minimally invasive esophagectomy: review of over 1000 patients. *Ann Surg*. 2012;256:95-103.
- Takeuchi H, Miyata H, Ozawa S, Udagawa H, Osugi H, Matsubara H, et al. Comparison of Short-Term Outcomes Between Open and Minimally Invasive Esophagectomy for Esophageal Cancer Using a Nationwide Database in Japan. *Ann Surg Oncol*. 2017;24:1821-7.
- Yibulayin W, Abulizi S, Lv H, Sun W. Minimally invasive oesophagectomy versus open esophagectomy for resectable esophageal cancer: a meta-analysis. *World J Surg Oncol*. 2016;14:304.
- van der Sluis PC, van der Horst S, May AM, Schippers C, Broseus LAA, Joore HCA, et al. Robot-assisted Minimally Invasive Thoracoscopic Esophagectomy Versus Open Transthoracic Esophagectomy for Resectable Esophageal Cancer: A Randomized Controlled Trial. *Ann Surg*. 2019;269:621-30.
- Ozkaya M, Ozdogan M, Ozyazici S, Das K, Onel S. Minimally Invasive Approach for Mid-Esophageal and A Giant Epiphrenic Diverticula: Case Report. *JCAM*. 2016;7:268-70.
- Kleinberg L, Gibson MK, Forastiere AA. Chemoradiotherapy for localized esophageal cancer: regimen selection and molecular mechanisms of radiosensitization. *Nat Clin Pract Oncol*. 2007;4:282-94.
- Stahl M, Stuschke M, Lehmann N, Meyer HJ, Walz MK, Seeber S, et al. Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. *J Clin Oncol*. 2005;23:2310-7.
- Bozzetti F. Nutritional support in patients with esophageal cancer. *Support Care Cancer*. 2010;18:41-50.