Chapter 2

Multimodal Treatment for Cancer of the Esophagus

Lucian Mocan, Ofelia Mosteanu, Teodora Pop,
Lucia Agoston-Coldea, Cornel Iancu,
Teodora Mocan and Furcea Luminita

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.70991

Abstract

There are about 500,000 new cases of cancer of the esophagus and 400,000 esophageal cancer-related deaths recorded annually around the world. The disease is three to four times more frequent in men than in women, being the sixth most common cancer and the fifth most frequent cancer-related death among men. The prognosis of esophageal cancer is quite poor, despite advances in surgical procedures (two-field and three-field lymph node dissection) and perioperative management, which is still controversial. The use of chemotherapy and radiotherapy in combination with surgery might be a new approach for future treatment. Progress in optical technology has led to the development of a new minimally invasive surgical approach for the treatment of esophageal cancer, namely esophagectomy.

Keywords: esophageal cancer, chemotherapy, surgery, radiotherapy, outcome

1. Introduction

There are about 500,000 new cases of cancer of the esophagus and 400,000 esophageal cancer-related deaths recorded annually around the world. The disease is three to four times more frequent in men than in women, being the sixth most common cancer and the fifth most frequent cancer-related death among men [1].

Even though esophageal cancer was not very common in Western populations, the incidence of esophageal adenocarcinoma and its related mortality have increased in the USA and certain European countries [2]. The incidence of adenocarcinomas involving the esophago-gastric junction, the distal esophagus and the gastric cardia has recorded a more significant increase [3]. The transition from squamous cell carcinoma to Barrett's metaplasia-associated adenocarcinoma in Western populations could have been determined by the increase in the incidence of obesity and obesity-induced reflux [4, 5].

There are two main subtypes of the disease, namely esophageal squamous cell carcinoma and esophageal adenocarcinoma. The most common causes of squamous cell carcinoma are tobacco and alcohol, and the most common causes of adenocarcinoma are tobacco, obesity and acid reflux [5]. There has been a major increase in the incidence of adenocarcinoma in North America and Europe, while squamous cell carcinoma is still the most common type of esophageal cancer in Asia [6].

The two subtypes of esophageal cancer have different clinical and biological characteristics. While squamous cell carcinomas occur in the middle or upper third of the esophagus, adenocarcinomas occur in the lower third of the esophagus. Abdominal lymph node metastasis is usually present in adenocarcinomas, and the incidence of cervical or upper mediastinal lymph node metastasis is more frequent in squamous cell carcinomas. Thus, the therapeutic approach is different for each subtype [7].

The prognosis of esophageal cancer is quite poor, despite advances in surgical procedures (two-field and three-field lymph node dissection) and perioperative management, which is still controversial [7]. The use of chemotherapy and radiotherapy in combination with surgery might be a new approach for future treatment. Progress in optical technology has led to the development of a new minimally invasive surgical approach for the treatment of esophageal cancer, namely esophagectomy. Long-term survival in resectable esophageal cancer is also influenced by definitive chemoradiotherapy [8]. Salvage esophagectomy is used in patients with esophageal cancer who were treated with chemoradiation as definitive therapy [9].

Although cancer of the esophagus is among the most common cancers in the world, there are few studies on this malignancy. There have been significant changes in the epidemiology of esophageal cancer in the past 30 years, with a striking increase in incidence in Western populations, where the number of adenocarcinomas has exceeded those of the squamous cell type [6]. On the other hand, squamous cell carcinoma is the most frequent subtype in Asian countries, mainly developing in the middle third of the esophagus, without any dramatic increase in the incidence of adenocarcinoma on this continent. New diagnostic, staging, and therapeutic options have improved survival rates for esophageal cancer.

Early stage adenocarcinoma of the esophagogastric junction (AEG) could be detected based on efficient screening for gastroesophageal reflux disease (GERD) and Barrett's metaplasia, which might be cured using endoscopic ablation or surgery [10].

The infection with *Helicobacter pylori* harboring the cagA gene seems to be associated with a reduced risk of esophageal adenocarcinoma [11, 12].

The potential role of COX-2 inhibitors in the effective chemoprevention of esophageal adenocarcinoma, characterized by COX-2 overexpression, is another aspect to be considered [13]. The types of surgery for cancer of the esophagus are divided based on the complex lymphatic drainage from the esophagus and gastric cardia and their anatomy.

http://dx.doi.org/10.5772/intechopen.70991

2. Esophageal resection

Hulscher et al. conducted a meta-analysis and obtained a 20% 5-year survival rate [14] following any of the two approaches. However, there were much higher rates of early morbidity and mortality in the case of transthoracic resection. On the other hand, in another study conducted by Hagen et al. [15], better survival rates (41% vs. 14%; $p < 0.001$) were obtained in 30 patients following en bloc esophagectomy compared with 39 patients undergoing transhiatal esophagectomy, suggesting the use of extended en bloc esophagectomy instead of transhiatal resection in the case of carcinoma of the lower third of the esophagus and gastric cardia [15].

Outcomes in esophageal cancer are often poor [16]. The best and most efficient surgical method in patients without evidence of spread to other parts of the body is the combination between esophagectomy and reconstruction surgery [7]. There are three more frequent minimally invasive techniques for esophagectomy: transhiatal esophagectomy, the Ivor Lewis esophagectomy (upper midline laparotomy combined with a right posterolateral thoracotomy), and the McKeown technique (right thoracotomy, upper midline laparotomy, and left neck incision). Several randomized trials compared transhiatal esophagectomy and standard transthoracic esophagectomy, showing no significant differences between them. The differences between transthoracic and transhiatal esophagectomy were examined in three randomized trials [17–21]. The results of these clinical trials showed no significant differences between the two approaches in what concerns patient survival. Hulscher et al. [22] conducted a randomized trial in patients with adenocarcinoma of the esophagus and gastric cardia (106 patients with transhiatal esophagectomy and 114 with transthoracic esophagectomy). There were lower morbidity rates in the case of transhiatal esophagectomy than in transthoracic esophagectomy with extended en bloc lymph node dissection. Despite the absence of statistically significant differences in terms of disease-free, median overall, and quality-adjusted survival, there was an improvement in long-term survival of patients with extended transthoracic resection. Asia, especially Japan, accounts for the majority of the more aggressive surgery records. Five-year survival rates following three-field lymph node dissection were 48.7% in a study conducted by Kato et al. [23] and 55.0% in a study by Akiyama et al. [24].

Esophagectomy can be either transhiatal or transthoracic, performed using the Ivor Lewis technique (combined laparotomy and right thoracotomy) and the modified McKeown procedure, involving laparotomy, right thoracotomy with neck anastomosis, left thoracotomy, or left thoracoabdominal incision [25]. The approach is chosen depending on tumor location and surgeon preferences. Good treatment outcomes result from the complexity of these surgical procedures, the experience of the surgeons, and intensive care resources [26].

A comprehensive randomized study assessing the differences between the transthoracic and the transhiatal approach indicated similar mortality rates for both procedures, whereas morbidity rates were lower for the transhiatal approach. The transthoracic group showed non-significant associations between this procedure and overall and disease-free survival. However, there was an improvement in locoregional disease-free survival following transthoracic esophagectomy in a subgroup of patients who did not present extensive nodal involvement [27].

Long-term survival rates following open esophagectomy do not differ significantly when comparing these surgical procedures, as shown by various meta-analyses and randomized trials [28]. In their study, Tabira et al. [29] recommended the use of three-field lymph node dissection in patients with one to four lymph node metastases. As indicated by Shiozaki et al. [30], neck dissection might be eliminated in patients with carcinoma in the middle or lower third of the esophagus without lymph node metastasis along the recurrent nerve chain. Lerut et al. [31] also proved an improvement in patient survival following three-field lymph node dissection.

When comparing three-field with two-field lymph node dissection for squamous cell carcinoma of the esophagus, Kato et al. obtained 5-year survival rates of 48.7% for the first approach and 33.7% for the second. However, this study was contested due to differences in patient characteristics. Isono et al. [32] conducted a nationwide study and obtained better survival rates when using three-field dissection instead of the two-field approach. Fujita et al. [33] also presented much better survival rates following three-field lymph node dissection ($p < 0.05$) for carcinoma in the upper or middle third of the esophagus spreading to the lymph nodes. Still, there were no differences in mortality, morbidity, and postoperative quality of life between the two approaches [33]. Radical esophagectomy helps remove ≥80 lymph nodes and 5-year survival rates are around 40–60% [34].

3. Minimally invasive surgery

Pulmonary complications after transthoracic esophagectomy are high. The minimally invasive thoracoscopic approach might result in lower morbidity and mortality rates. Being minimally invasive, thoracoscopy should replace the open approach. In a study conducted by Cuschieri et al. [35], the researchers performed right thoracoscopy (esophagectomy and lymph node dissection) in a small group of patients and paved the way for the future use of thoracoscopic esophagectomy. This procedure proved to be feasible and even superior to open surgery. Nevertheless, the first outcomes using this approach were not significantly better than those obtained with the open approach, mainly as a result of the great number of pulmonary complications [36–38]. However, a few medical research centers in Japan found a new stimulus. For example, Akaishi et al. [39] obtained good outcomes in 39 patients with cancer of the esophagus who underwent en bloc esophagectomy with radical lymph node dissection via right thoracoscopy, with the following parameters: 200±41 min operating time, 270±157 ml blood loss, and the number of harvested lymph nodes was 19.7±11. All patients survived and there was a modest decrease in vital capacity in 22 of them, without requiring postoperative ventilation. A significant finding of the study was that pulmonary complications were reduced compared with the open procedure.

In their study, Luketich et al. [40] proved that minimally invasive esophagectomy (MIE) is efficient and safe in the United States. The study was conducted on 1033 consecutive patients and results indicated a significantly lower mortality rate (0.9%), with an 8-day median hospital stay. In a study performed in the United Kingdom, Mamidanna et al. [41] assessed 7502 patients undergoing esophagectomy (E) and MIE ($n = 1.155$) and results showed no differences in terms of 30-day morbidity and mortality. MIE proved to be safe for use by professionals, without supplementary patient safety risks. Despite the low number of annual esophagectomies (2) per medical center, study results were similar and MIE was preferred in terms of perioperative outcomes. On the other hand, there are insufficient and incomplete cancer comparative research data. Certain centers noted higher lymph node retrieval following MIE with lymph node dissection [42–44], whereas others did not find any considerable differences [45]. In a study performed on 168 patients, Palazzo et al. [46] demonstrated that long-term survival was twice better in patients who underwent MIE (hazard ratio—2.0). Despite significant patient and tumor variables, there were concerns related to the ability to reproduce the major differences in results obtained for these groups. Additionally, the small number of patients might assign any variations to defective regulations.

In a study assessing three-field lymph node dissection, Osugi et al. compared 77 patients with squamous cell cancer who underwent minithoracotomy to 72 controls who underwent conventional three-stage treatment. Exceptional outcomes were obtained in terms of lymph node retrieval (33 vs. 32), operating time (227 vs. 186 min), reduced vital capacity (15% vs. 22%, $p = 0.016$), 3-year survival (70% vs. 60%), and 5-year survival (55% vs. 57%) [44]. Resection via thoracoscopy showed almost similar results to open esophagectomy. Moreover, surgical trauma was reduced. The differences in outcome between the first 34 and the next 46 patients who underwent surgery in the same study group demonstrated the impact of the learning curve on obtaining shorter operating times and better results by using this approach. Other advantage is that greater experience helps reduce postoperative pulmonary complications (5% incidence). Reduced blood loss, shorter operating time for thoracoscopy, reduced postoperative respiratory complications and higher lymph node retrieval were all observed in the last group [44]. In a study conducted on 222 patients undergoing thoracoscopic and laparoscopic esophageal resection, Luketich et al. (Ann Surg 2003; 238:486–494) showed an incidence rate of pneumonia of 7.7%. A significant finding was the reduced length of intensive care unit stay (1 day) and hospital stay (7 days) and the 1.4% operative mortality. Quality of life indicator was comparable to baseline scores and population standards. Nguyen et al. [47] assessed 46 consecutive patients and found similar results to Luketich et al. There have also been studies supporting robot-assisted thoracoscopy; however, there is still need for further investigation regarding robotic esophagectomy [48].

The results obtained by Biere et al. [49] in the TIME (Traditional Invasive vs. Minimally Invasive Esophagectomy) trial comparing the outcomes of 115 British patients who underwent either E or MIE showed that besides a decrease in perioperative pulmonary complications, the two procedures were more or less similar. However, the main competence of the trial was to show differences in short-term outcomes, with lower capacity in pointing out other outcomes. Patient outcomes were adapted to a population, improving the ability to perform a multivariate analysis of small differences in survival. There are few data on comparative differences in robot-assisted esophagectomy. In a study conducted on 43 patients who were treated with MIE (of which 11 underwent robot-assisted esophagectomy), Weksler et al. [50] reached the conclusion that robot-assisted and conventional procedures were similar. There were not enough patients included in the study, the results were disorganized, and there were no cancer data. Our study also experiences difficulties due to this aspect when comparing robotic with conventional MIE, but we managed to explain certain confounding variables for our outcomes. The limitations of our study are represented by the inability to determine specific MIE approaches (the McKeown procedure, the Ivor Lewis approach, and the transhiatal procedure). Earlier studies have demonstrated that the three procedures have similar outcomes, even though there are differences in terms of perioperative complications [51]. Another drawback was the difficulty in differentiating between patients who underwent hybrid procedures, such as laparoscopy combined with minithoracotomy, and patients who were treated with total MIE. These limitations pave the way for the occurrence of unknown interactions and confounding variables. Currently, there are two different clinical trials comparing E to MIE patients, namely the French MIRO trial [52] and the British ROMIRO trail [53]. Still, the study that we conducted is the most extensive comparative effectiveness research of MIE assessing long-term survival. As a result, MIE determines poor improvement in perioperative outcomes, with no negative impact on survival rates.

4. Combined modality therapy

4.1. Neoadjuvant chemotherapy

The use of preoperative chemotherapy compared with surgical treatment has been assessed in randomized trials in order to obtain improved surgical outcomes. However, the results are highly disputed. The three meta-analyses built on these randomized trials showed no difference in survival when the endpoint was 1-year survival in six of these trials. On the contrary, in comparison with surgical treatment, 2-year survival rates were improved following preoperative chemotherapy (4.4%) when the endpoint was 2-year survival in seven randomized trials [53]. When the meta-analysis was restricted to four recently randomized trials based on cisplatin and 5-fluorouracil therapy, there was a 6.3% improvement in 2-year survival. Still, this increase did not occur in one meta-analysis where the endpoint was 2-year survival [54]. The impact of preoperative chemotherapy is still uncertain.

4.2. Neoadjuvant chemoradiotherapy

Used in Europe and America since the end of the 1980s, preoperative chemoradiotherapy determined survival rate improvement in patients with cancer of the esophagus. Despite being used on a small scale due to the advanced surgical procedures available in Japan, a randomized trial reported the efficiency of hyperthermochemoradiotherapy in esophageal cancer [55]. Five meta-analyses built on five to seven randomized trials assess the impact of surgery alone, on the one hand, with preoperative chemoradiotherapy used in combination with surgery, on the other hand. There were no improvements in survival rates following preoperative chemoradiotherapy when the endpoint was 1-year or 2-year survival. When the endpoint was 3-year survival, there was an increase in perioperative mortality within 90 days after surgery, contrasted by a decrease in local recurrence and an improvement in 3-year survival rates in analogy to surgery alone (Int J Hyperthermia 1992; 8:289–295). There was a 14% decrease in death risk following preoperative chemoradiotherapy when the endpoint was the hazard ratio of survival curves [56]. Several reports [57–59] of six randomized trials showed higher survival rates following preoperative chemoradiotherapy than after surgery alone. Another report focusing on esophageal adenocarcinoma reported much higher survival rates following preoperative chemoradiotherapy versus surgery alone [60].

A meta-analysis of randomized trials conducted in Europe and America reported no improvement in survival with postoperative chemotherapy following curative resection in patients with cancer of the esophagus. In contrast, a randomized trial conducted in Japan showed that postoperative chemotherapy determined a major improvement in disease-free survival. In conclusion, postoperative chemotherapy recommends itself as an efficient measure to prevent recurrence after surgery.

4.3. Adjuvant radiotherapy

Four randomized trials assessing the differences between surgery alone and postoperative radiotherapy (45–65 Gy) reported no major improvements in survival. However, there was a decrease in local recurrence in the irradiated area following postoperative radiotherapy. No major improvements in survival were observed in a meta-analysis of these randomized trials. In conclusion, postoperative radiotherapy is not a conventional treatment option.

4.4. Postoperative outcome

The incidence of postoperative mortality was assessed in a considerable number of studies [61–65], fewer assessed in-hospital mortality, and 30-day mortality was determined in two studies [66]. Values were higher in patients who were treated with salvage esophagectomy after definitive chemoradiotherapy (23 patients—9.50%) than in patients who treated with planned esophagectomy after neoadjuvant chemoradiotherapy (29 patients—4.07%). Pooling of results validated the much higher incidence of postoperative mortality in the case of salvage esophagectomy (prevalence odds ratios (POR) = 3.02; 95% CI 1.64–5.58; $p < 0.001$).

Author details

Lucian Mocan[1,2]*, Ofelia Mosteanu[1,3], Teodora Pop[1,3], Lucia Agoston-Coldea[4], Cornel Iancu[1,2], Teodora Mocan[1,5] and Furcea Luminita[1,2]

*Address all correspondence to: lucian.mocan@umfcluj.ro

1 Regional Institute of Gastroenterology and Hepatology, “Prof. Dr. Octavian Fodor”, Cluj-Napoca, Romania

2 Department of Surgery, University of Medicine and Pharmacy, “Iuliu Hatieganu”, Cluj-Napoca, Romania

3 Department of Gastroenterology, University of Medicine and Pharmacy, “Iuliu Hatieganu”, Cluj-Napoca, Romania

4 Department of Internal Medicine, University of Medicine and Pharmacy, “Iuliu Hatieganu”, Cluj-Napoca, Romania

5 Department of Physiology, University of Medicine and Pharmacy, “Iuliu Hatieganu”, Cluj-Napoca, Romania

References

[1] Daly JM, Karnell LH, Menck HR. National Cancer Data Base report on esophageal carcinoma. Cancer. 1996;**78**(8):1820-1828

[2] PDQ Screening and Prevention Editorial Board. In: Anonymous, editor. Esophageal Cancer Screening (PDQ(R)): Health Professional Version. In PDQ Cancer Information Summaries. Bethesda (MD): National Cancer Institute; 2002

[3] Hosokawa Y, Kinoshita T, Konishi M, Takahashi S, Gotohda N, Kato Y, Daiko H, Nishimura M, Katsumata K, Sugiyama Y. Clinicopathological features and prognostic factors of adenocarcinoma of the esophagogastric junction according to Siewert classification: Experiences at a single institution in Japan. Annals of Surgical Oncology. 2012;**19**(2):677-683

[4] Spechler SJ. Barrett esophagus and risk of esophageal cancer: A clinical review. JAMA. 2013;**310**(6):627-636

[5] Duits LC, Phoa KN, Curvers WL, Ten Kate FJ, Meijer GA, Seldenrijk CA, Offerhaus GJ, Visser M, Meijer SL, Krishnadath KK, Tijssen JG, Mallant-Hent RC, Bergman JJ. Barrett's oesophagus patients with low-grade dysplasia can be accurately risk-stratified after histological review by an expert pathology panel. Gut. 2015;**64**(5):700-706

[6] Bray F, Ferlay J, Laversanne M, Brewster D, Gombe Mbalawa C, Kohler B, Piñeros M, Steliarova-Foucher E, Swaminathan R, Antoni S. Cancer incidence in five continents: Inclusion criteria, highlights from volume X and the global status of cancer registration. International Journal of Cancer. 2015;**137**(9):2060-2071

[7] Napier KJ, Scheerer M, Misra S. Esophageal cancer: A review of epidemiology, pathogenesis, staging workup and treatment modalities. World Journal of Gastrointestinal Oncology. 2014;**6**(5):112-120

[8] Chen M, Yang Y, Lai C, Chen P, Chen W. Outcome of patients with esophageal cancer: A nationwide analysis. Annals of Surgical Oncology. 2013;**20**(9):3023-3030

[9] Watanabe M, Mine S, Nishida K, Yamada K, Shigaki H, Matsumoto A, Sano T. Salvage esophagectomy after definitive chemoradiotherapy for patients with esophageal squamous cell carcinoma: Who really benefits from this high-risk surgery? Annals of Surgical Oncology. 2015;**22**(13):4438-4444

[10] Wang X, Fan J, Wang A, Leng Y, Li J, Bao Y, Wang Y, Yang Q, Ren Y. Epidemiology of esophageal cancer in Yanting-regional report of a national screening programme in China. Asian Pacific Journal of Cancer Prevention. 2013;**14**(4):2429-2432

[11] Hatakeyama M. Helicobacter pylori CagA and gastric cancer: A paradigm for hit-and-run carcinogenesis. Cell Host & Microbe. 2014;**15**(3):306-316

[12] Kandulski A, Venerito M, Malfertheiner P. Helicobacter pylori and esophageal neoplasia. In: Esophageal Cancer and Barrett's Esophagus. Wiley; 2015. p. 79-86

[13] Yusup G, Akutsu Y, Mutallip M, Qin W, Hu X, Komatsu-Akimoto A, Hoshino I, Hanari N, Mori M, Akanuma N. A COX-2 inhibitor enhances the antitumor effects of che motherapy and radiotherapy for esophageal squamous cell carcinoma. International Journal of Oncology. 2014;**44**(4):1146-1152

[14] Hulscher JB, Tijssen JG, Obertop H, van Lanschot, J, Jan B. Transthoracic versus transhiatal resection for carcinoma of the esophagus: A meta-analysis. The Annals of Thoracic Surgery 2001;**72**(1):306-313

[15] Hagen JA, Peters JH, DeMeester TR. Superiority of extended en bloc esophagogastrectomy for carcinoma of the lower esophagus and cardia. The Journal of Thoracic and Cardiovascular Surgery. 1993;**106**(5):850-858 discussion 858-9

[16] Chen M, Huang J, Zhu Z, Zhang J, Li K. Systematic review and meta-analysis of tumor biomarkers in predicting prognosis in esophageal cancer. BMC Cancer. 2013;**13**(1):1

[17] Chang AC, Ji H, Birkmeyer NJ, Orringer MB, Birkmeyer JD. Outcomes after transhiatal and transthoracic esophagectomy for cancer. The Annals of Thoracic Surgery. 2008;**85**(2): 424-429

[18] Nguyen NT, Follette DM, Wolfe BM, Schneider PD, Roberts P, Goodnight JE. Comparison of minimally invasive esophagectomy with transthoracic and transhiatal esophagectomy. Archives of Surgery. 2000;**135**(8):920-925

[19] Rentz J, Bull D, Harpole D, Bailey S, Neumayer L, Pappas T, Krasnicka B, Henderson W, Daley J, Khuri S. Transthoracic versus transhiatal esophagectomy: A prospective study of 945 patients. The Journal of Thoracic and Cardiovascular Surgery. 2003;**125**(5):1114-1120

[20] Stark SP, Romberg MS, Pierce GE, Hermreck AS, Jewell WR, Moran JF, Cherian G, Delcore R, Thomas JH. Transhiatal versus transthoracic esophagectomy for adenocarcinoma of the distal esophagus and cardia. The American Journal of Surgery. 1996;**172**(5):478-482

[21] Chu K, Law SY, Fok M, Wong J. A prospective randomized comparison of transhiatal and transthoracic resection for lower-third esophageal carcinoma. The American Journal of Surgery. 1997;**174**(3):320-324

[22] Hulscher JB, van Sandick JW, de Boer AG, Wijnhoven BP, Tijssen JG, Fockens P, Stalmeier PF, ten Kate FJ, van Dekken H, Obertop H: Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. The New England Journal of Medicine 2002;**347**(21):1662-1669

[23] Kato H, Watanabe H, Tachimori Y, Iizuka T. Evaluation of neck lymph node dissection for thoracic esophageal carcinoma. The Annals of Thoracic Surgery. 1991;**51**(6):931-935

[24] Akiyama H, Tsurumaru M, Udagawa H, Kajiyama Y. Radical lymph node dissection for cancer of the thoracic esophagus. Annals of Surgery. 1994;**220**(3):364-372 discussion 372-3

[25] Boone J, Livestro DP, Elias SG, Borel Rinkes IH, Van Hillegersberg R. International survey on esophageal cancer: Part I surgical techniques. Diseases of the Esophagus. 2009;**22**(3):195-202

[26] Daly JM, Fry WA, Little AG, Winchester DP, McKee RF, Stewart AK, Fremgen AM. Esophageal cancer: Results of an American College of Surgeons patient care evaluation study. Journal of the American College of Surgeons. 2000;**190**(5):562-572

[27] Omloo JM, Lagarde SM, Hulscher JB, Reitsma JB, Fockens P, van Dekken H, ten Kate FJ, Obertop H, Tilanus HW, van Lanschot JJ: Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the mid/distal esophagus: Five-year survival of a randomized clinical trial. Annals of Surgery 2007;**246**(6):992-1000; discussion 1000-1

[28] Pennathur A, Gibson MK, Jobe BA, Luketich JD. Oesophageal carcinoma. The Lancet. 2013;**381**(9864):400-412

[29] Tabira Y, Kitamura N, Yoshioka M, Tanaka M. Significance of three-field lymphadenectomy for carcinoma of the thoracic esophagus based on depth of tumor infiltration, lymph nodal involvement and survival rate. The Journal of Cardiovascular Surgery. 1999;**40**(5):737

[30] Shiozaki H, Yano M, Tsujinaka T, Inoue M, Tamura S, Doki Y, Yasuda T, Fujiwara Y, Monden M. Lymph node metastasis along the recurrent nerve chain is an indication for cervical lymph node dissection in thoracic esophageal cancer. Diseases of the Esophagus. 2001;**14**(3-4):191-196

[31] Lerut T, Nafteux P, Moons J, Coosemans W, Decker G, De Leyn P, Van Raemdonck D, Ectors N. Three-field lymphadenectomy for carcinoma of the esophagus and gastroesophageal junction in 174 R0 resections: Impact on staging, disease-free survival, and outcome: A plea for adaptation of TNM classification in upper-half esophageal carcinoma. Annals of Surgery. 2004;**240**(6):962-974

[32] Isono K, Sato H, Nakayama K. Results of a nationwide study on the three-field lymph node dissection of esophageal cancer. Oncology. 1991;**48**(5):411-420

[33] Fujita H, Kakegawa T, Yamana H, Shima I, Toh Y, Tomita Y, Fujii T, Yamasaki K, Higaki K, Noake T. Mortality and morbidity rates, postoperative course, quality of life, and prognosis after extended radical lymphadenectomy for esophageal cancer. Comparison of three-field lymphadenectomy with two-field lymphadenectomy. Annals of Surgery. 1995;**222**(5):654-662

[34] Nishimaki T, Suzuki T, Suzuki S, Kuwabara S, Hatakeyama K. Outcomes of extended radical esophagectomy for thoracic esophageal cancer. Journal of the American College of Surgeons. 1998;**186**(3):306-312

[35] Cuschieri A, Shimi S, Banting S. Endoscopic oesophagectomy through a right thoracoscopic approach. Journal of the Royal College of Surgeons of Edinburgh. 1992;**37**(1):7-11

[36] Dexter S, Martin I, McMahon M. Radical thoracoscopic esophagectomy for cancer. Surgical Endoscopy. 1996;**10**(2):147-151

[37] Robertson G, Lloyd D, Wicks A, Veitch P. No obvious advantages for thoracoscopic two-stage oesophagectomy. The British Journal of Surgery. 1996;**83**(5):675-678

[38] Law S, Fok M, Chu K, Wong J. Thoracoscopic esophagectomy for esophageal cancer. Surgery. 1997;**122**(1):8-14

[39] Akaishi T, Kaneda I, Higuchi N, Kuriya Y, Kuramoto J, Toyoda T, Wakabayashi A. Thoracoscopic en bloc total esophagectomy with radical mediastinal lymphadenectomy. The Journal of Thoracic and Cardiovascular Surgery. 1996;**112**(6):1533-1541

[40] Markar SR, Karthikesalingam A, Penna M, Low DE. Assessment of short-term clinical outcomes following salvage esophagectomy for the treatment of esophageal malignancy: Systematic review and pooled analysis. Annals of Surgical Oncology. 2014;**21**(3):922-931

[41] Mamidanna R, Bottle A, Aylin P, Faiz O, Hanna GB. Short-term outcomes following open versus minimally invasive esophagectomy for cancer in England: A population-based national study. Annals of Surgery. 2012;**255**(2):197-203

[42] Parameswaran R, Veeramootoo D, Krishnadas R, Cooper M, Berrisford R, Wajed S. Comparative experience of open and minimally invasive esophagogastric resection. World Journal of Surgery. 2009;**33**(9):1868-1875

[43] Singh RK, Pham TH, Diggs BS, Perkins S, Hunter JG. Minimally invasive esophagectomy provides equivalent oncologic outcomes to open esophagectomy for locally advanced (stage II or III) esophageal carcinoma. Archives of Surgery. 2011;**146**(6):711-714

[44] Osugi H, Takemura M, Higashino M, Takada N, Lee S, Ueno M, Tanaka Y, Fukuhara K, Hashimoto Y, Fujiwara Y. Learning curve of video-assisted thoracoscopic esophagectomy and extensive lymphadenectomy for squamous cell cancer of the thoracic esophagus and results. Surgical Endoscopy And Other Interventional Techniques. 2003; **17**(3):515-519

[45] Watanabe M, Baba Y, Nagai Y, Baba H. Minimally invasive esophagectomy for esophageal cancer: An updated review. Surgery Today. 2013;**43**(3):237-244

[46] Palazzo F, Rosato EL, Chaudhary A, Evans NR, Sendecki JA, Keith S, Chojnacki KA, Yeo CJ, Berger AC. Minimally invasive esophagectomy provides significant survival advantage compared with open or hybrid esophagectomy for patients with cancers of the esophagus and gastroesophageal junction. Journal of the American College of Surgeons. 2015;**220**(4):672-679

[47] Nguyen NT, Roberts P, Follette DM, Rivers R, Wolfe BM. Thoracoscopic and laparoscopic esophagectomy for benign and malignant disease: Lessons learned from 46 consecutive procedures. Journal of the American College of Surgeons. 2003;**197**(6):902-913

[48] Bodner JC, Zitt M, Ott H, Wetscher GJ, Wykypiel H, Lucciarini P, Schmid T. Robotic-assisted thoracoscopic surgery (RATS) for benign and malignant esophageal tumors. The Annals of Thoracic Surgery. 2005;**80**(4):1202-1206

[49] Biere SS, van Berge Henegouwen, Mark I, Maas KW, Bonavina L, Rosman C, Garcia JR, Gisbertz SS, Klinkenbijl JH, Hollmann MW, de Lange ES: Minimally invasive versus open oesophagectomy for patients with oesophageal cancer: A multicentre, open-label, randomised controlled trial. The Lancet 2012;**379**(9829):1887-1892

[50] Weksler B, Sharma P, Moudgill N, Chojnacki K, Rosato E. Robot-assisted minimally invasive esophagectomy is equivalent to thoracoscopic minimally invasive esophagectomy. Diseases of the Esophagus. 2012;**25**(5):403-409

[51] Pfister DG, Johnson DH, Azzoli CG, Sause W, Smith TJ, Baker S,Jr, Olak J, Stover D, Strawn JR, Turrisi AT, Somerfield MR, American Society of Clinical Oncology: American Society of Clinical Oncology treatment of unresectable non-small-cell lung cancer guideline: Update 2003. Journal of Clinical Oncology 2004;**22**(2):330-353

[52] Briez N, Piessen G, Bonnetain F, Brigand C, Carrere N, Collet D, Doddoli C, Flamein R, Mabrut JY, Meunier B, Msika S, Perniceni T, Peschaud F, Prudhomme M, Triboulet JP, Mariette C. Open versus laparoscopically-assisted oesophagectomy for cancer: a multicentre randomised controlled phase III trial—The MIRO trial. BMC Cancer. 2011;**11**: 310-2407-11-310

[53] Avery KN, Metcalfe C, Berrisford R, Barham CP, Donovan JL, Elliott J, Falk SJ, Goldin R, Hanna G, Hollowood AA. The feasibility of a randomized controlled trial of esophagectomy for esophageal cancer-the ROMIO (randomized oesophagectomy: Minimally invasive or open) study: Protocol for a randomized controlled trial. Trials. 2014;**15**(1):1

[54] Urschel JD, Vasan H, Blewett CJ. A meta-analysis of randomized controlled trials that compared neoadjuvant chemotherapy and surgery to surgery alone for resectable esophageal cancer. The American Journal of Surgery. 2002;**183**(3):274-279

[55] Sugimachi K, Kitamura K, Baba K, Ikebe M, Morita M, Matsuda H, Kuwano H. Hyperthermia combined with chemotherapy and irradiation for patients with carcinoma of the oesophagus—A prospective randomized trial. International Journal of Hyperthermia. 1992;**8**(3):289-295

[56] Greer SE, Goodney PP, Sutton JE, Birkmeyer JD. Neoadjuvant chemoradiotherapy for esophageal carcinoma: A meta-analysis. Surgery. 2005;**137**(2):172-177

[57] Urba SG, Orringer MB, Turrisi A, Iannettoni M, Forastiere A, Strawderman M. Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal carcinoma. Journal of Clinical Oncology. 2001;**19**(2):305-313

[58] Bosset J, Gignoux M, Triboulet J, Tiret E, Mantion G, Elias D, Lozach P, Ollier J, Pavy J, Mercier M. Chemoradiotherapy followed by surgery compared with surgery alone in squamous-cell cancer of the esophagus. The New England Journal of Medicine. 1997; **337**(3):161-167

[59] Prise EL, Etienne PL, Meunier B, Maddern G, Hassel MB, Gedouin D, Boutin D, Campion JP, Launois B. A randomized study of chemotherapy, radiation therapy, and surgery versus surgery for localized squamous cell carcinoma of the esophagus. Cancer. 1994;**73**(7):1779-1784

[60] Enzinger PC, Mayer RJ. Esophageal cancer. The New England Journal of Medicine. 2003;**349**(23):2241-2252

[61] Chao Y, Chan S, Chang H, Liu Y, Wu Y, Hsieh M, Tseng C, Liu H. Salvage surgery after failed chemoradiotherapy in squamous cell carcinoma of the esophagus. European Journal of Surgical Oncology (EJSO). 2009;**35**(3):289-294

[62] Marks JL, Hofstetter W, Correa AM, Mehran RJ, Rice D, Roth J, Walsh G, Vaporciyan A, Erasmus J, Chang J. Salvage esophagectomy after failed definitive chemoradiation for esophageal adenocarcinoma. The Annals of Thoracic Surgery. 2012;**94**(4):1126-1133

[63] Miyata H, Yamasaki M, Takiguchi S, Nakajima K, Fujiwara Y, Nishida T, Mori M, Doki Y. Salvage esophagectomy after definitive chemoradiotherapy for thoracic esophageal cancer. Journal of Surgical Oncology. 2009;**100**(6):442-446

[64] Morita M, Kumashiro R, Hisamatsu Y, Nakanishi R, Egashira A, Saeki H, Oki E, Ohga T, Kakeji Y, Tsujitani S. Clinical significance of salvage esophagectomy for remnant or recurrent cancer following definitive chemoradiotherapy. Journal of Gastroenterology. 2011;**46**(11):1284-1291

[65] Smithers B, Cullinan M, Thomas J, Martin I, Barbour A, Burmeister B, Harvey J, Thomson D, Walpole E, Gotley D. Outcomes from salvage esophagectomy post definitive chemoradiotherapy compared with resection following preoperative neoadjuvant chemoradiotherapy. Diseases of the Esophagus. 2007;**20**(6):471-477

[66] Takeuchi H, Saikawa Y, Oyama T, Ozawa S, Suda K, Wada N, Takahashi T, Nakamura R, Shigematsu N, Ando N. Factors influencing the long-term survival in patients with esophageal cancer who underwent esophagectomy after chemoradiotherapy. World Journal of Surgery. 2010;**34**(2):277-284