

Infectious complications after esophagectomy for esophageal cancer

Subjects: Surgery

Submitted by:  Hiroya

Takeuchi

(This entry belongs to Entry Collection "Gastrointestinal Disease")

Definition

Despite advances in the perioperative management of esophagectomy, it is still a highly invasive procedure for esophageal cancer and is associated with severe postoperative complications. The two major postoperative infectious complications after esophagectomy are pulmonary complications and anastomotic leakage.

1. Introduction

Esophageal cancer is the sixth leading cause of cancer-related mortality globally because of its high malignant potential and poor prognosis [1]. The postoperative 5-year survival rate in patients with American Joint Committee on Cancer stage I esophageal cancer is approximately 90%. This rate decreases to 45%, 20%, and 10% in patients with stages II, III, and IV diseases, respectively [2]. Esophagectomy is still the most effective treatment option, although chemoradiotherapy may be effective in treating esophageal cancer treatment [3]. Despite developments in extended lymph node dissection and perioperative management of esophagectomy, it remains a highly invasive procedure associated with severe postoperative complications [4]. The Japanese national database, including 5354 esophagectomy patients in 713 hospitals in 2011, indicated an overall morbidity rate of 41.9% and a 30-day and surgery-related mortality of 1.2% and 3.4%, respectively [5].

The effect of postoperative complications on long-term survival has been investigated in many cancers [4][6], including a recent meta-analysis of colorectal cancer studies [7]. Some reports have shown the adverse effect of postoperative esophagectomy complications on long-term survival [4][8], whereas others have reported that postoperative esophagectomy complications did not affect long-term survival [9]. We previously conducted a meta-analysis to investigate the effect of postoperative complications after esophagectomy on long-term survival [10].

The two major postoperative infectious complications after esophagectomy are pulmonary complications and anastomotic leakage [11].

2. The Effect of Postoperative Complications after Esophagectomy for Cancer on Survival

2.1. Pulmonary Complications

Using information recorded between 2011 and 2012 from a nationwide database in Japan, we reported that the rate of pulmonary complications after esophagectomy was 14.8% (1419/9584) [5]. Additionally, Ancona et al., reported that postoperative pulmonary complications (25.2%, 110/437) after esophagectomy did not affect long-term survival [12]. However, Baba et al., and Saeki et al., recently reported postoperative pulmonary complications (19.7%, 99/502 and 10.2%, 59/580, respectively) after esophagectomy had a significant negative effect on long-term survival [13][14].

We previously reported that, within a single institution, postoperative pneumonia after esophagectomy (22.5%, 64/284) had a significant negative effect on overall survival (OS) ($p = 0.035$). Furthermore, multivariate analysis revealed that the presence of pneumonia was predictive of poorer OS; the multivariate hazard ratio (HR) was 1.456 (95% confidence interval (CI) 1.020–2.079, $p = 0.039$)⁴.

Furthermore, we analyzed the data from a randomized controlled trial (JCOG9907 trial); the OS of patients with pneumonia (14.5%, 22/152) was shorter than that of patients without pneumonia (HR: 1.82, 95% CI: 1.01–3.29), and progression-free survival (PFS) tended to be shorter in patients with pneumonia (HR: 1.50, 95% CI: 0.85–2.62) [8]. Additionally, we conducted a meta-analysis to investigate the impact of pulmonary complications after esophagectomy on survival [10]. Patients with pulmonary complications had significantly worse five-year OS (HR: 1.37, 95% CI: 1.16–1.62, $p = 0.0003$), five-year cancer-specific survival (CSS) (HR: 1.60, 95% CI: 1.35–1.89, $p < 0.00001$), and five-year disease-free survival (DFS) (HR: 1.18, 95% CI: 1.00–1.38, $p = 0.04$).

2.2. Anastomotic Leakage

Using information recorded between 2011 and 2012 from a nationwide database in Japan, we reported that the anastomotic leakage rate after esophagectomy was 12.6% (1203/9584) [5]. Additionally, Markar et al., reported that using a multicenter database in France, postoperative severe anastomotic leakage (8.5%, 208/2439) negatively affected long-term survival significantly [15].

In contrast, we previously reported that, in a single institution, anastomotic leakage after esophagectomy (19.4%, 55/284) did not affect OS [4]. Furthermore, we analyzed data from the JCOG9907 trial; OS of patients with anastomotic leakage (13.8%, 21/152) was nearly identical to that of patients without leakage (HR: 1.06, 95% CI: 0.52–2.13); PFS showed the same tendency (HR: 1.28, 95% CI: 0.71–2.32) [8]. However, we conducted a meta-analysis to investigate the impact of anastomotic leakage after esophagectomy on survival and reported that patients with anastomotic leakage had significantly worse five-year OS (HR: 1.18, 95% CI: 1.04–1.33, $p = 0.01$), five-year CSS (HR: 1.81, 95% CI: 1.11–2.95, $p = 0.02$), and five-year DFS (HR: 1.13, 95% CI: 1.03–1.25, $p = 0.01$) [10].

2.3. Overall Complications

Using information recorded between 2011 and 2012 from a nationwide database in Japan, we reported that the rate of overall morbidity after esophagectomy was 42.8% (4102/9584) [5]. Ancona et al., and Ferri et al., reported that overall postoperative complications did not affect long-term survival (16.3%, 85/522 and 22.6%, 98/434, respectively) [12][16]. However, Baba et al., and Saeki et al., recently reported that overall postoperative complications negatively affected long-term survival (43.2%, 217/502 and 26.6%, 154/580, respectively) [13][14].

We conducted a meta-analysis to investigate the impact of overall morbidity after esophagectomy on survival and reported that the overall postoperative morbidity had significantly worse five-year OS (HR: 1.16, 95% CI: 1.06–1.26, $p = 0.001$) and five-year CSS (HR: 1.28, 95% CI: 1.11–1.48, $p = 0.0009$) [10].

It was possible that the worsening of the general condition after postoperative complications lead to a delay or cessation of additional therapy after esophagectomy and led to esophageal cancer recurrence [4].

3. Clinical Significance of Proinflammatory Cytokines

Persistent infection or chronic inflammation significantly contributes to tumorigenesis and tumor progression. C-X-C motif ligand 8 (CXCL8) is a chemokine that acts as an important multifunctional cytokine to modulate tumor proliferation, invasion, and migration in an autocrine or paracrine manner [17]. CXCL8 and its cognate receptors, C-X-C chemokine receptor 1 (CXCR1) and C-X-C chemokine receptor 2 (CXCR2), may mediate the initiation and development of various cancers, including breast cancer [18], prostate cancer [19], lung cancer [20], colorectal carcinoma [21], and melanoma [22]. Further, CXCL8 integrates with multiple intracellular signaling pathways to produce coordinated effects. Additionally, neovascularization, which provides a basis for fostering tumor growth and metastasis, is now recognized as a critical function of CXCL8 in the tumor microenvironment [17].

The complication-specific factors that negatively affected long-term survival included pulmonary

complications, involving a generalized infection that produced strong impairment of the immunological system leading to esophageal cancer recurrence [4]. Furthermore, we previously reported that infectious postoperative esophagectomy complications significantly increased the levels of inflammatory cytokines, such as CXCL6 and CXCL8 [23]. Increased expression of CXCL8 and its receptor, CXCR2, has been correlated with tumor progression after esophagectomy [24][25]. Thus, pulmonary complications may be related to tumor progression by promoting inflammatory cytokines, such as CXCL8, which negatively affects CSS and DFS [4]. Additionally, anastomotic leakage could result in the spread of viable tumor cells locally from stapled or sutured anastomoses. Locoregional recurrence after anastomotic leakage could be related to a proinflammatory response that promotes tumor growth [15]. Pulmonary infectious complications and anastomotic leakage have been related to tumor progression by developing inflammatory cytokines, such as CXCL8 [10]. Moreover, anastomotic leakage after esophagectomy have been shown to negatively affect CSS and DFS.

References

1. Sung, H.; Ferlay, J.; Siegel, R.L.; Laversanne, M.; Soerjomataram, I.; Jemal, A.; Bray, F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries 2021. *CA Cancer J. Clin.* 2021, 71, 209–249.
2. Ando, N.; Ozawa, S.; Kitagawa, Y.; Shinozawa, Y.; Kitajima, M. Improvement in the results of surgical treatment of advanced squamous esophageal carcinoma during 15 consecutive years. *Ann. Surg.* 2000, 232, 225–232.
3. Cooper, J.S.; Guo, M.D.; Herskovic, A.; Macdonald, J.S.; Martenson, J.A., Jr.; Al-Sarraf, M.; Byhardt, R.; Russell, A.H.; Beitler, J.J.; Spencer, S.; et al. Chemoradiotherapy of locally advanced esophageal cancer: Long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. *JAMA* 1999, 281, 1623–7162.
4. Booka, E.; Takeuchi, H.; Nishi, T.; Matsuda, S.; Kaburagi, T.; Fukuda, K.; Nakamura, R.; Takahashi, T.; Wada, N.; Kawakubo, H.; et al. The Impact of Postoperative Complications on Survivals After Esophagectomy for Esophageal Cancer. *Medicine* 2015, 94, e1369.
5. Takeuchi, H.; Miyata, H.; Gotoh, M.; Kitagawa, Y.; Baba, H.; Kimura, W.; Tomita, N.; Nakagoe, T.; Shimada, M.; Sugihara, K.; et al. A Risk Model for Esophagectomy Using Data of 5354 Patients Included in a Japanese Nationwide Web-Based Database. *Ann. Surg.* 2014, 260, 259–266.
6. Tokunaga, M.; Tanizawa, Y.; Bando, E.; Kawamura, T.; Terashima, M. Poor survival rate in patients with postoperative intra-abdominal infectious complications following curative gastrectomy for gastric cancer. *Ann. Surg. Oncol.* 2013, 20, 1575–1583.
7. McSorley, S.T.; Horgan, P.G.; McMillan, D.C. The impact of the type and severity of postoperative complications on long-term outcomes following surgery for colorectal cancer: A systematic review and meta-analysis. *Crit. Rev. Oncol. Hematol.* 2016, 97, 168–177.
8. Kataoka, K.; Takeuchi, H.; Mizusawa, J.; Igaki, H.; Ozawa, S.; Abe, T.; Nakamura, K.; Kato, K.; Ando, N.; Kitagawa, Y. Prognostic impact of postoperative morbidity after esophagectomy for esophageal cancer: Exploratory analysis of JCOG9907. *Ann. Surg.* 2017, 265, 1152–1157.
9. Martin, L.W.; Swisher, S.G.; Hofstetter, W.; Correa, A.M.; Mehran, R.J.; Rice, D.C.; Vaporciyan, A.A.; Walsh, G.L.; Roth, J.A. Intrathoracic leaks following esophagectomy are no longer associated with increased mortality. *Ann. Surg.* 2005, 242, 392–399.
10. Booka, E.; Takeuchi, H.; Suda, K.; Fukuda, K.; Nakamura, R.; Wada, N.; Kawakubo, H.; Kitagawa, Y. Meta-analysis of the impact of postoperative complications on survival after oesophagectomy for cancer. *BJS Open* 2018, 2, 276–284.
11. Takeuchi, H.; Miyata, H.; Ozawa, S.; Udagawa, H.; Osugi, H.; Matsubara, H.; Konno, H.; Seto, Y.; Kitagawa, Y. 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, 1821–1827.
12. Ancona, E.; Cagol, M.; Epifani, M.; Cavallin, F.; Zaninotto, G.; Castoro, C.; Alfieri, R.; Ruol, A. Surgical Complications Do Not Affect Longterm Survival after Esophagectomy for Carcinoma of the Thoracic Esophagus and Cardia. *J. Am. Coll. Surg.* 2006, 203, 661–669.
13. Baba, Y.; Yoshida, N.; Shigaki, H.; Iwatsuki, M.; Miyamoto, Y.; Sakamoto, Y.; Watanabe, M.; Baba, H. Prognostic impact of postoperative complications in 502 patients with surgically resected esophageal squamous cell carcinoma: A retrospective single-institution study. *Ann. Surg.* 2016, 264, 305–311.
14. Saeki, H.; Tsutsumi, S.; Tajiri, H.; Yukaya, T.; Tsutsumi, R.; Nishimura, S.; Nakaji, Y.; Kudou, K.; Akiyama, S.; Kasagi, Y.; et al. Prognostic Significance of Postoperative Complications After Curative Resection for Patients with Esophageal Squamous Cell Carcinoma. *Ann. Surg.* 2017, 265, 527–533.
15. Markar, S.; Gronnier, C.; Duhamel, A.; Mabrut, J.-Y.; Bail, J.-P.; Carrere, N.; Lefevre, J.H.; Brigand, C.; Vaillant, J.-C.; Adham, M.; 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, 972–980.
16. Ferri, L.E.; Law, S.; Wong, K.H.; Kwok, K.F.; Wong, J. The influence of technical complications on postoperative outcome and survival after esophagectomy. *Ann. Surg. Oncol.* 2006, 13, 557–564.
 17. Liu, Q.; Li, A.; Tian, Y.; Wu, J.D.; Liu, Y.; Li, T.; Chen, Y.; Han, X.; Wu, K. The CXCL8-CXCR1/2 pathways in cancer. *Cytokine Growth Factor Rev.* 2016, 31, 61–71.
 18. Zuccari, D.A.P.D.C.; Leonel, C.; Castro, R.; Gelaleti, G.B.; Jardim, B.V.; Moscheta, M.G.; Regiani, V.R.; Ferreira, L.C.; Lopes, J.R.; Neto, D.D.S.; et al. An immunohistochemical study of interleukin-8 (IL-8) in breast cancer. *Acta Histochem.* 2012, 114, 571–576.
 19. Araki, S.; Omori, Y.; Lyn, D.; Singh, R.K.; Meinbach, D.M.; Sandman, Y.; Lokeshwar, V.B.; Lokeshwar, B.L. Interleukin-8 Is a Molecular Determinant of Androgen Independence and Progression in Prostate Cancer. *Cancer Res.* 2007, 67, 6854–6862.
 20. Masuya, D.; Huang, C.; Liu, D.; Kameyama, K.; Hayashi, E.; Yamauchi, A.; Kobayashi, S.; Haba, R.; Yokomise, H. The intratumoral expression of vascular endothelial growth factor and interleukin-8 associated with angiogenesis in nonsmall cell lung carcinoma patients. *Cancer* 2001, 92, 2628–2638.
 21. Brew, R.; Erikson, J.S.; West, D.C.; Kinsella, A.R.; Slavin, J.; Christmas, S.E. Interleukin-8 as an autocrine growth factor for human colon carcinoma cells in vitro. *Cytokine* 2000, 12, 78–85.
 22. Singh, S.; Varney, M.; Singh, R.K. Host CXCR2-dependent regulation of melanoma growth, angiogenesis, and experimental lung metastasis. *Cancer Res.* 2009, 69, 411–415.
 23. Okamura, A.; Takeuchi, H.; Matsuda, S.; Ogura, M.; Miyasho, T.; Nakamura, R.; Takahashi, T.; Wada, N.; Kawakubo, H.; Saikawa, Y.; et al. Factors Affecting Cytokine Change After Esophagectomy for Esophageal Cancer. *Ann. Surg. Oncol.* 2015, 22, 3130–3135.
 24. Ogura, M.; Takeuchi, H.; Kawakubo, H.; Nishi, T.; Fukuda, K.; Nakamura, R.; Takahashi, T.; Wada, N.; Saikawa, Y.; Omori, T.; et al. Clinical significance of CXCL-8/CXCR-2 network in esophageal squamous cell carcinoma. *Surgery* 2013, 154, 512–520.
 25. Inoue, M.; Takeuchi, H.; Matsuda, S.; Nishi, T.; Fukuda, K.; Nakamura, R.; Takahashi, T.; Wada, N.; Kawakubo, H.; Kitagawa, Y. IL-8/CXCR2 signalling promotes cell proliferation in oesophageal squamous cell carcinoma and correlates with poor prognosis. *Anticancer. Res.* 2021, 41, 783–794.

Keywords

postoperative complication;esophageal cancer;esophagectomy;CXCL8;CXCR2