Infectious complications after esophagectomy for esophageal cancer

Subjects: Surgery

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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.

Keywords: postoperative complication ; esophageal cancer ; esophagectomy ; CXCL8 ; CXCR2

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.

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