Abstract

Esophagectomy is the main treatment for esophageal cancer. The 2 histologic subtypes of esophageal cancer are squamous cell carcinoma and adenocarcinoma; these subtypes have different biologic features and treatment strategies. Although the prognosis of patients treated with surgery alone remains unsatisfactory, neoadjuvant therapy helps to improve outcome. A meta-analysis revealed that neoadjuvant chemoradiotherapy provides survival benefits for both histologic types, while neoadjuvant chemotherapy is useful for adenocarcinoma. In Western countries, neoadjuvant chemoradiotherapy is a standard treatment for resectable advanced esophageal cancer, while neoadjuvant chemotherapy has become the standard treatment in Japan. Esophagectomy can be performed by several different approaches, including McKeown (cervico-thoraco-abdominal), Ivor-Lewis (thoraco-abdominal), and transthiatal approaches. It has been suggested that Minimally Invasive Esophagectomy (MIE) contributes to the reduction of pulmonary complications. Cervico-thoraco-abdominal 3-field lymphadenectomy may prolong survival, but a randomized control study on this subject has not been conducted. Mortality and morbidity rates after esophagectomy remain high. Several meta-analyses demonstrated that esophagectomy at low-volume hospitals was associated with a significant increase in the incidence of in-hospital and 30-day mortality. The influence of hospital volume on long-term outcome continues to be a subject of debate.

In conclusion, surgical resection remains the main treatment for potentially curable esophageal cancer. Neoadjuvant treatment can improve long-term outcome after esophagectomy. Furthermore, MIE may improve short-term outcome, and 3-field lymph node dissection may reduce the risk of recurrence. The effects of these surgical procedures should be confirmed by randomized prospective studies.

Keywords: Esophageal cancer; Esophagectomy; Outcomes

Introduction

Esophageal cancer is highly aggressive; therefore, a multimodality approach is required to cure this disease. Surgical resection remains the mainstay among the modalities. In this review, we discuss the role of esophagectomy for esophageal cancer treatment and describe the results from recent esophageal cancer surgery reports.

Overview

An estimated 482,300 new esophageal cancer cases and 406,800 esophageal cancer-related deaths occurred worldwide in 2008 [1]. Esophageal cancer is 3 to 4 times more common among males than among females, and it is the sixth most frequent cancer (326,600) and the fifth most common cause of cancer death (276,100) among men [1]. The 2 major histologic subtypes are squamous cell carcinoma and adenocarcinoma. Risk factors for squamous cell carcinoma include smoking and excessive alcohol consumption [2], while smoking, obesity, and gastroesophageal reflux disease are the major risk factors for adenocarcinoma [3,4]. Recently, the incidence of adenocarcinoma has been significantly increasing in North America and Europe [5]. In contrast, squamous cell carcinoma remains the most frequent histologic subtype in Asian countries.

The clinical features and biologic behavior of the 2 histologic subtypes are different. Squamous cell carcinoma is frequently located in the mid-esophagus and tends to spread to the cervical, mediastinal, and abdominal lymph nodes [6,7]. Adenocarcinoma frequently occurs in the lower esophagus and gastric cardia. Metastasis to the abdominal lymph nodes is usually observed in this histologic type, and the incidence of cervical or upper mediastinal lymph node metastasis is less frequent than that in squamous cell carcinoma. Therefore, several differences exist in the treatment strategies between the 2 histologic subtypes.
while the JES guidelines are based on the Japanese Classification of Esophageal Cancer.

Surgical resection remains the mainstay of potentially curable esophageal cancer. However, trials of adjuvant chemotherapy or radiotherapy have been conducted to improve survival because the long-term outcomes of patients treated with surgery alone are unsatisfactory. To date, no study has proven that postoperative adjuvant therapy has a survival benefit [13]; thus, recent trials have focused on neoadjuvant treatment. Meta-analyses on neoadjuvant treatment for esophageal cancer have provided strong evidence that neoadjuvant chemoradiotherapy provides a greater survival benefit than surgery alone for both squamous cell carcinoma and adenocarcinoma [13-15]. Likewise, neoadjuvant chemotherapy provided an obvious survival benefit for adenocarcinoma, but its benefit for squamous cell carcinoma is still controversial [15].

According to these findings, the NCCN guidelines recommend preoperative chemoradiotherapy for T2 or higher tumors. Neoadjuvant chemotherapy is also recommended for adenocarcinoma in this group. Definitive chemoradiotherapy is an option, especially for cervical esophageal cancer. The ESMO guidelines also recommend preoperative chemoradiotherapy for T3–4 cases. Regarding the response to neoadjuvant chemo(radio)therapy, further chemoradiation resulted in an overall survival that was equivalent to surgery in patients with squamous cell carcinoma, despite an increase in local recurrence (French and German Phase III study) [16,17]. Therefore, definitive chemoradiotherapy is an option for neoadjuvant treatment responders. A European study group demonstrated that perioperative (both preoperative and postoperative) chemotherapy significantly improved the survival of patients with lower esophageal or esophagogastric adenocarcinoma (MAGIC trial) [18]. Accordingly, the ESMO guidelines recommend perioperative chemotherapy for patients with adenocarcinoma.

In Japan, surgeons attempted to improve the survival of patients with advanced esophageal cancer by extended radical lymphadenectomy [19-21]. Favorable long-term outcomes have been achieved in Japan because of improvements to surgical procedures. Thus, attention has been focused on adjuvant chemotherapy to control micrometastasis. A clinical study in Japan revealed that adjuvant chemotherapy improved the disease-free survival of patients with node-positive clinical stage II/III squamous cell carcinoma (ICCG 9204) [22]. A recent follow-up study clarified that the overall survival of patients treated with neoadjuvant chemotherapy followed by surgery was significantly better than that of patients treated with surgery followed by chemotherapy (ICCG 9907) [23]. Based on these findings, the current standard treatment for resectable advanced squamous cell carcinoma of the esophagus is neoadjuvant chemotherapy followed by esophagectomy in Japan.

**Surgical approaches**

Several different approaches exist for esophagectomy (Table 1). Conventionally, the standard procedures have been thoracoabdominal or transhiatal open esophagectomy. Recently, Minimally Invasive Esophagectomy (MIE) using thoracoscopy and/or laparoscopy has been developed to reduce the surgical stress of esophagectomy.

**McKeown esophagectomy (3-phase esophagectomy):** This method includes subtotal esophagectomy through right thoracotomy with anastomosis of the cervical esophagus to the stomach brought to the neck. This approach allows the greatest longitudinal and radical margins, permits complete lymphadenectomy, and minimizes the risk of intrathoracic leak. Cervico-thoraco-abdominal 3-field lymph node dissection can be performed with this approach.

**Ivor-Lewis esophagectomy (through laparotomy and right thoracotomy):** Ivor-Lewis esophagectomy consists of middle and lower esophagectomy through right thoracotomy with anastomosis of the intrathoracic esophagus to the stomach at the level of the azygos arch. This approach is used typically for patients with tumors of the middle or lower third of the esophagus. This approach allows complete resection of the tumor with an extended thoracoabdominal lymphadenectomy, prevents complications with a safe and simple technique, and provides excellent digestive comfort with a high intrathoracic anastomosis.

**Transhiatal esophagectomy:** Transhiatal esophagectomy is a subtotal esophagectomy by transhiatal dissection combined with transcervical dissection without thoracotomy. Reconstruction is performed with a gastric tube through the esophageal bed with cervical esophagogastric anastomosis. The benefits of this approach include limited surgical trauma, reduced operative time, and less frequent respiratory complications and mortality. Because the oncological quality of resection is compromised by insufficient mediastinal clearance, this approach is frequently performed for early staged tumors or tumors located in the esophagogastric junction. Both a large-scale cohort and a meta-analysis comparing transthoracic with transhiatal esophagectomy demonstrated that transhiatal esophagectomy was associated with significantly reduced operative time, length of hospital stay, postoperative respiratory complications, and early mortality [24,25].

**Minimally invasive esophagectomy (MIE):** Minimally invasive approaches have been incorporated into esophageal cancer surgery in order to improve the postoperative outcomes of esophagectomy [26]. Several authors have demonstrated that total MIE using a combined thoracoscopic and laparoscopic approach can be performed safely, but the short-term outcome benefits of this approach remain controversial [27-29]. Oncologic outcomes are favorable, and MIE may have an advantage over open esophagectomy in terms of lymph node dissection [30,31]. The benefits of MIE should be confirmed by randomized control studies.

**Salvage esophagectomy**

Salvage esophagectomy is defined as esophagectomy for remnant or relapsed tumors after definitive chemoradiotherapy. Although definitive chemoradiotherapy is a treatment with curative potential, locoregional failure remains a major problem and 40% to 60% of patients have recurrent locoregional disease [32,33]. Although salvage esophagectomy has the potential to cure these patients, the major problems of this approach are high morbidity and mortality
rates [34-36]. Anastomotic leakage and pulmonary insufficiency are observed frequently after salvage esophagectomy, and the reported hospital mortality ranges from 3% to 22.2% [34-36]. Therefore, salvage esophagectomy should be considered for carefully selected patients at specialized centers.

**Short-term outcome of esophagectomy**

Esophagectomy is a highly invasive surgery for which high morbidity and mortality rates have been reported. A large-scale prospective cohort at multiple Veterans Administration hospitals between 1991 and 2001 demonstrated a 9.8% mortality rate and a 49.5% morbidity rate [37]. In this report, the most frequent postoperative complications were pneumonia (21%), respiratory failure (16%), and ventilator support for more than 48 hours (22%).

Cervico-thoraco-abdominal 3-field lymph node dissection is the most radical lymphadenectomy procedure for esophageal cancer. It has become a standard surgical procedure in Japan, and has been adopted in some Western high-volume centers [38,39]. The reported mortality and morbidity rates of esophagectomy with 3-field lymphadenectomy are shown in Table 2 [21,38-43]. Although the frequency of recurrent laryngeal nerve paralysis was high after 3-field dissection, the mortality rates of this procedure appear to be comparable to those of conventional esophagectomy when it is performed in high-volume centers.

The potential advantages of centralizing esophageal and other high-risk cancer surgeries are recent topics of discussion in many healthcare systems. Several meta-analyses demonstrated that esophagectomy at low-volume hospitals was associated with a significant increase in the incidence of in-hospital and 30-day mortality [44,45]. In order to improve short-term outcomes after esophagectomy, centralization to specialized hospitals is essential.

Whether or not MIE improves short-term outcomes after esophagectomy remains a controversial subject. One of the expected merits of MIE is improved short-term outcomes, especially reduced pulmonary complications. Some authors reported that compared to open esophagectomy, MIE significantly decreased pulmonary morbidity rates [46-48], while other authors demonstrated comparable pulmonary morbidity rates between MIE and open esophagectomy [49-51]. Recent randomized control trial which compared MIE with open esophagectomy revealed that pulmonary infection within 2 weeks after surgery was fewer in the MIE group than in the open group [52]. Further trials are needed to confirm the result.

### Table 2: Morbidity and mortality after esophagectomy with 3-field lymphadenectomy.

| Authors               | Journal        | Year | Stage | Setting* | No. | Morbidity (%) | Pneumonia RLNP* | Leak | Mortality (%) |
|-----------------------|----------------|------|-------|----------|-----|---------------|-----------------|------|---------------|
| Baba, et al. [40]     | Ann Surg       | 1994 | I–III | S        | 106 | 23.6          | 41.5            | 28.3 | 10.3          |
| Fujita, et al. [21]   | Ann Surg       | 1995 | I–III | CRT+S   | 63  | 27.0          | 69.8            | 33.3 | 2.0           |
| Udagawa, et al. [41]  | Dis Esophagus  | 2001 | I–III | S        | 530 | 12.5          | 12.5            | 6.8***| 2.8           |
| Altorki, et al. [38]  | Ann Surg       | 2002 | I–III | CRT+S   | 80  | 8.7           | 13.8            | 11.3 | 3.75          |
| Tachibana, et al. [42]| Ann Surg       | 2005 | I–III | S        | 141 | 21.3          | 28.4            | 25.5 | 6.4           |
| Ferahköse, et al. [36]| Dis Esophagus  | 2006 | I–III | S        | 46  | 41.4          | 13.0            | 28.0 | 6.5           |
| Nakamura, et al. [43] | Langenbech Arch Surg | 2008 | I–III | S        | 104 | 19.6          | 1.6**           | 9.2  | 3.2           |

*RLNP, Recurrent laryngeal nerve palsy; **permanent paralysis; ***Major leak

| Authors               | Journal        | Year | Stage | Setting* | No. | Morbidity (%) | Survival (%) | MST **(M) |
|-----------------------|----------------|------|-------|----------|-----|---------------|--------------|-----------|
| Bosset, et al. [53]   | N Engl J Med  | 1997 | I–III | S        | 139 | 138           | 18.6         |          |
|                       |                |      |       | CRT+S   |     |               |              |           |
| Kelsen, et al. [54]   | N Engl J Med  | 1998 | I–III | S        | 234 | 233           | 16.1         |          |
|                       |                |      |       | CRT+S   |     |               |              |           |
| MRCOCWG* [55]        | Lancet         | 2002 | Selectable | S      | 437 | 434           | 13.3         |          |
|                       |                |      |       | CRT+S   |     |               |              |           |
| Ando et al. [22]      | J Clin Oncol   | 2003 | II–III | S        | 122 | 52            |              |          |
|                       |                |      |       | S+CT     |     |               |              |          |
| Burmeister, et al. [56]| Lancet Oncol  | 2005 | I–III | S        | 128 | 128           | 19.3         |          |
|                       |                |      |       | CRT+S   |     |               |              |           |
| Stahl, et al. [16]    | J Clin Oncol   | 2005 | II–III | S        | 86  | 86            | 16.4         |          |
|                       |                |      |       | CRT+S   |     |               |              |           |
| Bedonne, et al. [17]  | J Clin Oncol   | 2007 | II–III | S        | 234 | 233           | 15.6         |          |
|                       |                |      |       | CRT+S   |     |               |              |           |
| Kelsen et al [57]    | J Clin Oncol   | 2007 | II–III | S        | 402 | 400           | 17.1         |          |
|                       |                |      |       | CRT+S   |     |               |              |           |
| Allum et al. [58]    | J Clin Oncol   | 2009 | Selectable | S      | 319 | 319           | 54.0         |          |
|                       |                |      |       | CRT+S   |     |               |              |           |
| Ando et al. [23]      | Ann Surg Oncol | 2011 | II–III | S+CT     | 164 | 166           | 55           |          |
|                       |                |      |       |         |     |               |              |          |
| Ozawa, et al. [59]   | Esophagus      | 2012 | Registry | 0      | 25  | 363           | 91.3         | 85.9    |
|                       |                |      |       | I       |     |               |              |          |
|                       |                |      |       | IIA     | 363 | 297           | 86.4         | 79.1    |
|                       |                |      |       | IIB     | 297 | 262           | 54.0         | 55.8    |
|                       |                |      |       | III     | 319 | 319           | 41.8         |          |
|                       |                |      |       | IV      | 319 | 319           | 34.2         | 27.7    |
|                       |                |      |       |         |     |               |              |          |

*S, surgery; CRT, chemoradiotherapy; CT, chemotherapy; dCRT, definitive chemoradiotherapy. **MST, median survival time. ***MRCOCWG, Medical Research Council Oesophageal Cancer Working Group

### Table 3: Long-term outcome after esophagectomy in large-scale clinical studies and a comprehensive registry in Japan, 2003.

**Survival (%)**

| Journal    | Year | Setting* | No. | Survival (%) | MST **(M) |
|------------|------|----------|-----|--------------|-----------|
| N Engl J Med | 1997 | S        | 139 | 18.6         |          |
| Lancet     | 2002 | Selectable | S | 13.3         |          |
| J Clin Oncol | 2003 | II–III | S+CT | 15.6 |          |
| Lancet Oncol | 2005 | I–III | S+CT | 19.3 |          |
| J Clin Oncol | 2005 | II–III | S+CT | 16.4 |          |
| J Clin Oncol | 2007 | II–III | S+CT | 15.6 |          |
| J Clin Oncol | 2009 | Selectable | S | 17.1 |          |
| Ann Surg Oncol | 2011 | II–III | S+CT | 55 |          |
| Esophagus | 2012 | Registry | 0 | 85.9 |          |
|           |      |          | I  | 79.1 |          |
|           |      |          | IIA| 55.8 |          |
|           |      |          | IIB| 41.8 |          |
|           |      |          | III| 27.7 |          |
|           |      |          | IV | 6.9  |          |
Long-term outcome of esophagectomy

Long-term outcome after esophagectomy differs among countries or institutes. The survival results of esophagectomy from large-scale clinical studies and from a comprehensive registry in Japan in 2003 are shown in Table 3 [16,17,22,23,53-59]. Although the tumor stage and background factors differed among patients, long-term outcomes were better in Japanese studies and in the Japanese registry compared to the other studies. The finding that outcomes were better in Japan may result from differences in the quality of lymph node dissection because 3-field lymphadenectomy is a standard procedure in Japan. Large-scale prospective randomized trials are required to provide conclusive evidence that differences in outcome are due to differences in the quality of lymph node dissection.

The influence of hospital volume on long-term outcomes after esophagectomy remains a topic of debate [44,45]. Further analysis is required to provide conclusive evidence of this influence.

Conclusion

Surgical resection remains the main treatment for potentially curable esophageal cancer. Neoadjuvant treatment can improve long-term outcome after esophagectomy. Furthermore, MIE may improve short-term outcome, and 3-field lymph node dissection may reduce the risk of recurrence. The effects of these surgical procedures should be confirmed by randomized prospective studies.

References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, et al. (2011) Global cancer statistics. CA Cancer J Clin 61: 69-90.
2. Morita M, Kumashiro R, Kubo N, Nakashima Y, Yoshida R, et al. (2010) Alcohol drinking, cigarette smoking, and the development of squamous cell carcinoma of the esophagus: epidemiology, clinical findings, and prevention. Int J Oncol 15: 126-134.
3. Ryan AM, Duong M, Healy L, Ryan SA, Parekh N, et al. (2011) Obesity, metabolic syndrome and esophageal adenocarcinoma: epidemiology, etiology and new targets. Cancer Epidemiol 35: 309-319.
4. El-Serag H (2008) The association between obesity and GERD: a review of the epidemiological evidence. Dig Dis Sci 53: 2307-2312.
5. Simard EP, Ward EM, Siegel R, Jemal A (2012) Cancers with increasing incidence trends in the United States: 1999 through 2008. CA Cancer J Clin.
6. Kinoshita I, Ohashi I, Nakagawa K et al. (1976) Lymph node metastasis in esophageal cancer: with special reference to the upper mediastinum and measures for its treatment. Jpn J Gastroenterol Surg 9: 424-430. (in Japanese)
7. Sannoe Y, Hiratsuksu R, Doki K (1981) Lymph node metastases in cancer of the thoracic esophagus. Am J Surg 141: 216-218.
8. Sobin LH, Gospodarowics M, Wittekind C (2009) Union InternationaleContre le Cancer. Oesophagus including oesophagogastric junction. TNM classification of malignant tumours. 7th ed. ‘Wiley-Blackwell, NY'.
9. Japan Esophageal Society (2007) Japanese classification of esophageal cancer. Tenth edition. Kanehana& Co., Ltd., Tokyo.
10. National Comprehensive Cancer Network. (2011) NCCN clinical practice guidelines in oncology. Esophageal and esophageal-gastric junction cancers version. Version 2.2011.
11. Stahl M, Budach W, Meyer HJ, Cervantes A; ESMO Guidelines Working Group (2010) Esophageal cancer: Clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 21: V64-V69.
12. Japan Esophageal Society (2012) Diagnostic and treatment guidelines for esophageal cancer. April 2012. Kanehara& Co., Ltd., Tokyo. (in Japanese)
13. Malthaner RA, Wong RK, Rumble RB, Zuraw L (2004) Neoadjuvant or adjuvant therapy for resectable esophageal cancer: a systematic review and meta-analysis. BMC Med 2: 35.
35. Gardner-Thorpe J, Hardwick RH, Dweryhouse SJ (2007) Salvage esophagectomy after local failure of definitive chemoradiotherapy. Br J Surg 94: 1059-1066.

36. Tachimori Y (2009) Role of salvage esophagectomy after definitive chemoradiotherapy. Gen Thorac Cardiovasc Surg 57: 71-78.

37. Bailey SH, Bull DA, Harpole DH, Rentz JJ, Neumayer LA, et al. (2003) Outcomes after esophagectomy: A ten-year prospective cohort. Ann Thorac Surg 75: 217-222.

38. Altorki N, Kent M, Ferrara C, Port J (2002) Three-field lymph node dissection for squamous cell and adenocarcinoma of the esophagus. Ann Surg 236: 177-183.

39. Ferahköşe Z, Anadol AZ, Gökbayır H, Dursun A, Oztürk E (2006) Three-field lymph node dissection in the treatment of thoracic esophageal carcinoma: the Turkish experience. Dis Esophagus 19: 232-237.

40. Baba M, Aikou T, Yoshinaka H, Natsugoe S, Fukumoto T, et al. (1994) Long-term results of subtotal esophagectomy with three-field lymphadenectomy for carcinoma of the thoracic esophagus. Ann Surg 219: 310-316.

41. Udagawa H, Akiyama H (2001) Surgical treatment of esophageal cancer: Tokyo experience of the three-field technique. Dis Esophagus 14: 110-114.

42. Tachibana M, Kinugasa S, Yoshimura H, Shibakita M, Tonomoto Y, et al. (2005) Clinical outcomes of extended esophagectomy with three-field lymph node dissection for esophageal squamous cell carcinoma. Am J Surg 189: 98-109.

43. Nakamura M, Iwahashi M, Nakamori M, Ishida K, Naka T, et al. (2008) An analysis of the factors contributing to a reduction in the incidence of pulmonary complications following an esophagectomy for esophageal cancer. Langenbecks Arch Surg 393: 127-133.

44. Wouters MW, Gooiker GA, van Sandick JW, Tollenaar RA (2012) The volume-outcome relationship in surgery for esophageal malignancy: Systematic review and meta-analysis. Cancer 118: 1754-1763.

45. Markar SR, Karthikesalingam A, Thrumurthy S, Low DE (2012) Volume-outcome relationship in surgery for esophageal malignancy: Systematic review and meta-analysis 2000-2011. J Gastrointest Surg 16: 1055-1063.

46. Fabian T, Martin JF, McKeelvey AA, Federico JA (2008) Minimally invasive esophagectomy: a teaching hospital's first year experience. Dis Esophagus 21: 220-225.

47. Schoppmann SF, Prager G, Langer FB, Riegler FM, Kabon B, et al. (2010) Open versus minimally invasive esophagectomy: a single-center case controlled study. Surg Endosc 24: 3044-3053.

48. Nafteux P, Moons J, Coosemans W, Decaluwé H, Decker G, et al. (2011) Minimally invasive oesophagectomy: a valuable alternative to open oesophagectomy for the treatment of early oesophageal and gastro-oesophageal junction carcinoma. Eur J Cardiothorac Surg 40: 1455-1465.

49. Osugi H, Takemura M, Higashino M, Takada N, Lee S, et al. (2003) A comparison of video-assisted thoracoscopic oesophagectomy and radical lymph node dissection for squamous cell cancer of the oesophagus with open operation. Br J Surg 90: 108-113.

50. Smithers BM, Golley DC, Martin I, Thomas JM (2007) Comparison of the outcomes between open and minimally invasive esophagectomy. Ann Surg 245: 232-240.

51. Mamidanna R, Bottle A, Aylin P, Faiz O, Hanna GB (2012) Short-term outcomes following open versus minimally invasive esophagectomy for cancer in England: A population-based national study. Ann Surg 255: 197-203.

52. Biere SS, van Berge Henegouwen MI, Maas KW, Bonavina L, Rosman C, et al. (2012) Minimally invasive versus open oesophagectomy for patients with oesophageal cancer: a multicenter, open-label, randomised controlled trial. Lancet 379: 1897-1892.

53. Bosset JF, Gignoux M, Triboulet JP, Tret E, Mantion G, et al. (1997) Chemoradiotherapy followed by surgery compared with surgery alone in squamous-cell cancer of the esophagus. N Engl J Med 337: 161-167.

54. Kelsen DP, Ginsberg R, Paiak TF, Sheahan DG, Gunderson L, et al. (1998) Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. N Engl J Med 339: 1979-1984.

55. Medical Research Council Oesophageal Cancer Working Group (2002) Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomised controlled trial. Lancet 359: 1727-1733.

56. Burmeister BH, Smithers BM, Gebski V, Fitzgerald L, Simes RJ, et al. (2005) Surgery alone versus chemoradiotherapy followed by surgery for resectable cancer of the oesophagus: a randomised controlled phase III trial. Lancet Oncol 6: 659-668.

57. Kelsen DP, Winter KA, Gunderson LL, Mortimer J, Estes NC, et al. (2007) Long-term results of RTOG Trial 8911 (USA Intergroup 113): A random assignment trial comparison of chemotherapy followed by surgery compared with surgery alone for esophageal cancer. J Clin Oncol 25: 3719-3725.

58. Allum WH, Stingl SP, Bancelwicz J, Clark PI, Langley RE (2009) Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer. J Clin Oncol 27: 5062-5067.

59. Ozawa S, Tachimori Y, Baba H, et al. (2011) Comprehensive registry of esophageal cancer in Japan, 2003. Esophagus 8: 9-29.