Abstract Advanced esophageal tumors have been a challenge for surgery since the very beginning, and these challenges continue still today. In the early period of three-field lymphadenectomy (late 1980s), there was no special attention paid to tracheal necrosis after such an extended operation. In 1988, we reported functional mediastinal dissection preserving the right bronchial artery to prevent such complications. In 1993, we reported that the survival after three-field lymphadenectomy was better than that after en-bloc esophagectomy, and then the lymph node compartment classification based on the metastatic rate and the survival rate. This concept was introduced into the 9th edition of the Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus published in 1999. In early 1980s, combined resection of the neighboring organs was initiated for a locally advanced esophageal cancer. Almost all patients who underwent such an operation, however, died of metastasis in the short-term after surgery without any additional treatment. In 1987, we reported several types of tracheal repair using the latissimus dorsi muscle flap, as a less-invasive surgery that enabled adjuvant or additive therapy, after resection of the trachea involved by cancer. Then in 2004, we demonstrated that the canine aorta could be resected even immediately after aortic stenting. This suggests that an esophageal cancer involving the aorta can be resected using a new technique. To meet the challenges posed by advanced esophageal cancer, the help of other specialized fields besides esophageal surgery is needed: “The specialist must know everything of something, something of everything.”

Keywords Advanced esophageal cancer · Three-field lymphadenectomy · Combined resection of the neighboring organs · History of esophageal cancer surgery

Introduction Surgical treatment for esophageal cancer has been a challenge for advanced tumors since the beginning, and challenges continue still. Today we would like to follow in the footsteps of predecessors to explore these challenges for advanced esophageal cancers, and then to introduce our work in Keio University, in the University of Occupational and Environmental Health, and in Kurume University.

In the late 1970s, when I was studying esophageal cancer under Associate Professor Kakegawa of Keio University, it had been very difficult preoperatively to find metastasis in the mediastinal and abdominal lymph nodes since computed tomography and the ultrasonography were not yet available. The extent of lymphadenectomy was then limited to within the lower mediastinum and the upper abdomen. In 1984, we reported the pattern of recurrence after esophagectomy for cancer in operations performed during the period from 1959 to 1978 at Keio University [1]. Sixteen patients (31 %) had metastasis in the lymph nodes among 51 patients who underwent an autopsy within 3 months after esophagectomy. Recurrence was most common in the upper mediastinum even with cancers in the middle and lower thoracic esophagus, as well as with cancers in the cervical and upper thoracic esophagus. In this study, we estimated the survival rate improved to be 5 % by extended resection of locally advanced tumors,
10% by extended lymphadenectomy for cervicothoracoabdominal three field dissection, and 20% by a combination of both procedures.

**Challenges to lymph node metastasis**

Before three-field lymphadenectomy

Lymph node metastasis in esophageal cancers had been noticed from the beginning of the history of surgical treatment for esophageal cancer in Japan. In 1933, Seo of Kyoto University reported on regional lymph nodes in each location of the esophagus based on the autopsy studies [3]. Findings reported here are now acceptable.

The birth of three-field lymphadenectomy

In 1976, Kinoshita and Kajitani [4] of the Cancer Institute Hospital initially started to resect the lymph nodes in the upper mediastinum, and reported the incidence of metastasis to lymph nodes along the recurrent laryngeal nerves being 32% (30/95). In 1981, Sannohe et al. [5] of Fukuoka University was the first to perform systematic dissection of the cervical lymph nodes, and reported a high incidence of metastasis in the supraclavicular lymph nodes. In 1986, at 5 years after publication of Sannohe’s report, more outcomes after cervicothoracoabdominal three-field lymphadenectomy were reported from several major centers of esophageal cancers in Japan.

Safety of three-field lymphadenectomy

During the period from late 1980s to early 1990s, there was some controversy over the extent of lymphadenectomy. Extended lymphadenectomy in the upper mediastinum was occasionally done through upper median sternotomy [6]. The trachea was completely isolated to resect the pretracheal lymph nodes, as well as the paratracheal lymph nodes during extended radical lymphadenectomy in some institutions [7]. In those days, the right bronchial artery was commonly resected together with the azygos arch, and also the pulmonary branches of the right vagus nerve were frequently resected during lymphadenectomy [8]. There was nothing unusual about ischemic lesions in the trachea and on occasion tracheal necrosis after such operations.

We next investigated the blood flows in the trachea. The tissue blood flow of the canine trachea was decreased to one-third of control level after transection of the bilateral bronchial arteries [9]. It was decreased to 20% of control after dissection of the whole circumference of the mediastinal trachea in addition of transection of the bilateral bronchial arteries; however, nothing in the trachea was observed in three of four dogs given this operation, except for an ischemic stricture in the trachea observed in one dog. Blood flow was decreased to 10% of control after dissection of the whole circumference of the cervical and mediastinal trachea in addition to the transection of the bilateral bronchial arteries, when tracheal necrosis with perforation or ischemic stricture in the trachea was observed in all five dogs. On the other hand, in those dogs in which the right bronchial artery was preserved, a decreased tissue blood flow in the trachea remained at around half the control level even after dissection of the whole circumference of the cervical and mediastinal trachea in addition to the transection of the left bronchial artery. Nothing in the trachea was observed in three of four dogs given this operation, except for ischemic stricture in the trachea observed in one dog. Thus in 1988, we reported functional mediastinal dissection preserving the right bronchial artery and pulmonary branches of the right vagus nerve [10]. Then in 2001, we reported a procedure preserving the right bronchial artery, the pulmonary branches of the right vagus nerve, the thoracic duct and the azygos arch as functional three-field dissection for esophageal cancer [11].

Efficacy of three-field lymphadenectomy

In 1991, Isono and colleagues [12] in Chiba University reported the efficacy of three-field lymphadenectomy based on enquiry research covering all the country. Three-field lymphadenectomy was then performed in only one-third of 96 hospitals registered in this research project in Japan. The study demonstrated that three-field lymphadenectomy improved the five-year survival rate by 8% compared with two-field lymphadenectomy. In the same year, Kato and colleagues [13] in the National Cancer Center Japan reported results from a prospective non-randomized trial that three-field lymphadenectomy improved the 5-year survival rate by 15%. In 1994, Akiyama and colleagues [14] in Toranomon Hospital reported a 20% increase in the 5-year survival rate after three-field lymphadenectomy. We compared the survivals after two-field and three-field lymphadenectomy in Kurume University with that after en-bloc esophagectomy in the Technical University of Munich. En-bloc esophagectomy was at the time considered to be the most extended radical esophagectomy in the world. In 1993, we reported that the 5-year survival rate after three-field lymphadenectomy was better by 20% than those after en-bloc esophagectomy and after two-field lymphadenectomy [15]. This survival benefit was, however, observed only in cancers in the upper or middle
Thoracic esophagus with lymph node metastasis. In 1994, the extent of lymphadenectomy was discussed in a consensus meeting of the International Society for Diseases of the Esophagus (ISDE), and classified into four types as standard, extended, total mediastinal, and three-field [17]. In 2003, we reported the survival rates after each of these four types of lymphadenectomy, and the survival after three-field lymphadenectomy was better than that after any other type of lymphadenectomy for cancers in the upper or middle thoracic esophagus with lymph node metastasis, while such survival benefit by three-field lymphadenectomy was not observed in cancers in the lower thoracic esophagus or in those cases without lymph node metastasis [18].

Standardization of three-field lymphadenectomy

In 1993, we initially reported the lymph node compartment classification based on the metastatic rate in each lymph node station and the survival rate after resection of those metastases [19, 20]. For example, cervical, upper mediastinal, paraesophageal, and paracardiac lymph nodes were defined as the Compartment-1 nodes which must be resected in every case having a cancer of the middle thoracic esophagus. According to this classification, the survival curve for each of the three lymph node compartments is clearly separated, and significant differences are observed among these three survival curves.

With increasing numbers of patients undergoing three-field lymphadenectomy, the conventional lymph node classification described in the 8th edition of the Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus, which had not changed since its first edition [21], was considered to be out-of-date for clinical use. The Japanese Society for Esophageal Diseases (JSED) organized a lymph node committee to establish a new lymph node classification for cancers in the thoracic esophagus based on outcomes after three-field lymphadenectomy. Sugimachi of Kyushu University, as chairman of the committee, proposed the new lymph node classification in 1996. The new classification was published in the 9th edition of the Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus [22] in 1999. Subsequently, three-field lymphadenectomy has been recognized as a standard surgical procedure for esophageal cancer in Japan.

In the 10th edition of the Japanese Classification of Esophageal Cancer [23], the successor of the Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus, published in 2007, the lymph node classifications for cancers in the cervical esophagus and for those at the esophagogastric junction based on our lymph node compartment theory were described [24, 25]. The lymph node classifications for all locations of esophageal cancer were thus completed. The photograph here shows the esophageal surgeons who contributed to this establishment of three-field lymphadenectomy (Fig. 1).

Challenge to locally advanced esophageal cancers

Combined resection of the neighboring organs

In 1980s, combined resection of the neighboring organs such as the aorta and the trachea in cases with a locally advanced esophageal cancer was initiated by several esophageal surgeons including Kawahara in the University of Occupational and Environmental Health, Kabuto in

Fig. 1 Esophageal surgeons to establish three-field lymphadenectomy

Osaka Medical Center for Cancer and Cardiovascular Diseases, and others [26, 27]. The surgical stress with such operations was too large to perform adjuvant or additive treatment soon after surgery. Almost all patients died of distant metastasis within a half a year [28]. It was considered that the earliest possible adjuvant or additive treatment after surgery was required to improve the long-term survival of patients who underwent such operations. In order to establish a less invasive surgical procedure to resect the trachea affected by cancer, we performed an experimental study to repair a defect in the canine trachea using the latissimus dorsi muscle flap. This animal experiment revealed that a defect within one-third of the circumference in the posterior wall of the trachea, namely a defect limited to within the tracheal membrane, could be repaired by the muscle flap without any tracheal stenosis; however, a defect affecting more than half the circumference of the posterior wall of the trachea or a defect in the anterior wall of the trachea resulted in tracheal stenosis due to tracheomalasia [29]. In 1987, we reported many types of tracheal repair using the latissimus dorsi muscle flap after resection of the trachea during esophagectomy for cancer [30].

Kurume trials on multimodal treatment for T4 esophageal cancer

In the 1990s, there was some controversy over which offered a better survival for patients with a locally advanced T4 esophageal cancer, neo-adjuvant chemoradiotherapy versus adjuvant chemoradiotherapy. During the period from 1993 to 1998 in Kurume University, we performed a prospective non-randomized trial based on patient’s own choice after informed consent comparing esophagectomy followed by chemoradiotherapy versus chemoradiotherapy followed by esophagectomy for T4 esophageal cancer. In 2005, we reported that chemoradiotherapy followed by esophagectomy offered better survival compared to esophagectomy followed by chemoradiotherapy [31]. In the same year, we reported the result after a prospective non-randomized trial comparing chemoradiotherapy with surgery versus without surgery for a locally advanced T4 esophageal cancer which was performed during the period from 1994 to 2002. This trial showed that surgery did not offer any survival benefit for responders to neo-adjuvant chemoradiotherapy, but might offer a survival benefit for non-responders [32]. It seemed that esophagectomy as salvage surgery was preferred for non-responders for chemoradiotherapy for T4 esophageal cancers. Thus, it was described in the Guidelines for Diagnosis and Treatment of Carcinoma of the Esophagus [33] published in 2007 that chemoradiotherapy was a standard treatment for locally advanced T4 esophageal cancers. It is now considered that salvage surgery is an optional treatment for non-responders, in other words for a residual tumor or for recurrence.

New concept and techniques to treat locally advanced esophageal cancers

We noted that surgery did not exceed chemoradiotherapy in the treatment for a T4 esophageal cancer. However, the 5-year survival rate after chemoradiotherapy for T4 tumors is about 10% [34]. To meet this challenge, new concepts and techniques must be introduced in this field, as earlier mentioned concerning resection of the trachea. We performed an animal experiment to resect the aorta affected by esophageal cancer. In 2004, Sasahara and colleagues [35] in Kurume University reported that the canine aorta could be resected even immediately after aortic stenting, as well as 3 days after that. After such procedure, dogs could survive more than a year without any complication. In 2011, Matono and colleagues [36] in Kurume University reported three patients who underwent aortic stenting due to aortic complications including a fistula and an aneurysm after esophagectomy for cancer. This suggests that an esophageal cancer involving the aorta even after definitive chemoradiotherapy can be resected using new techniques such as aortic stenting.

Past, present, and future of esophageal surgery

The history of esophageal surgery in Japan can be classified into three periods (Fig. 2). In the first period from 1930s to 1970s, transthoracic esophagectomy was achieved by positive pressure ventilation under tracheal intubation, and then transthoracic esophagectomy expanded all over the country. The concept, namely the paradigm, of the first era was safety. Almost all esophageal cancers were so advanced that preoperative radiotherapy was needed for down-staging of tumors. In the second period from the 1970s to the 1990s, radical esophagectomy with lymphadenectomy was achieved by advances in diagnostic techniques including endoscopy and in perioperative managements including assisted ventilation, nutritional support, bronchial toileting using bronchoscopy, and others. The paradigm of the second era was radicality, as represented by three-field lymphadenectomy and combined resection of the neighboring organs. In the third period from the 1990s to the present, low mortality and morbidity rates have been achieved by less-invasive treatments including endoscopic surgery, thoracoscopic and laparoscopic surgery, definitive chemoradiotherapy, and others. The paradigm of this third era is the quality of life. Multimodality therapy is now the mainstay in the treatment for esophageal cancers.
According to the Cancer Statistics 2012 in Japan, 11,669 people died of esophageal cancer in 2007 [37]. This year, the prevalence of esophageal cancer is estimated to be 19,994 people [38]. The gross mortality rate of esophageal cancer was, therefore, about 58 % because more than half of esophageal cancers were not resectable. The outcome after treatment for esophageal cancers is not going to be improved without challenging advanced tumors. Figure 3 shows the relationship between the time course and the volume of the problems to be resolved, which is interpreted as the survival rate [39]. As cited before, many problems concerning lymph node metastasis have been solved by the efforts of our predecessors; however, the 5-year survival rate is not yet over 50 % in cases with lymph node metastasis, and problems such as metastasis to the distant lymph nodes and metastases to multiple lymph nodes are not yet solved. The treatment for locally advanced T4 esophageal cancers has only just started. That for metastasis to the distant organs has not yet started. In other words, there remain several challenges concerning cases with a locally advanced T4 esophageal cancer and with metastasis to distant organs. The help of other specialized fields besides esophageal surgery is needed: “The specialist must know everything of something, something of everything.”

The challenge now in the treatment for advanced esophageal cancers consists of systemic metastasis and the local extension of tumors. There is nothing to treat systemic metastasis but to wait for some advance in chemoradiotherapy, molecular target drugs or other concepts. Salvage surgery or adjuvant surgery might be adopted for these patients. On the other hand, extended, but less invasive, surgery might hold some potential for locally advanced T4 esophageal cancers after introducing innovative techniques developed in cardiovascular surgery or in pulmonary surgery. Seishu Hanaoka, a Japanese surgeon in the Edo era (1760–1835) who first succeeded to resect a breast cancer under general anesthesia, is cited as follows [40]; “Patients who underwent resection of a breast cancer must have a relapse unless an axillary tumor is treated. Surgeons in future must challenge to this disease.”
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References

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