A History of Surgery for Locally-Advanced (T4) Cancer of the Thoracic Esophagus in Japan and a Personal Perspective

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The history of esophageal surgery in Japan can be divided into three periods, an era of safety from 1930 to 1980, an era of radicality from 1980 to 2000, and the era of quality of life (QOL) from 2000 to the present. The treatment for T4 cancers of the thoracic esophagus has also changed over time from preoperative radiotherapy, combined resection of the neighboring organs with esophagectomy, and to definitive chemoradiotherapy (dCRT) with salvage surgery. At present, almost all patients with an unresectable T4 esophageal cancer receive dCRT. However, there are many patients with a residual or recurrent tumor after dCRT. Salvage surgery for such patients often results in incomplete resection of the tumor because the tumor involves the trachea and/or aorta. New techniques to enable the resection of such neighboring organs even during salvage surgery are needed. In the future, the mainstay of treatment for esophageal cancer will be CRT with the foreseeable progress in new drugs and new techniques of radiotherapy. Surgery will be indicated for a local failure after CRT, while combined resection of the neighboring organs will be necessary to treat a local failure after CRT for T4 cancers. New surgical techniques have to be developed through some application of new devices and equipment.

Keywords: history, locally-advanced T4 esophageal cancer, combined resection, definitive chemoradiotherapy, salvage surgery

Introduction

In 1909, Melzer and Auer,1) an immigrant from Germany and a German American, invented positive pressure ventilation under tracheal intubation. In 1914, Torek,2) an immigrant from Russia educated at the University of Berlin, was the first to successfully resect a cancer in the thoracic esophagus through a left thoracotomy in the New York German Hospital under general anesthesia according to Melzer-Auer.

In 1933, Seo3) in the Chiba University, reported a two-stage operation – esophagectomy through a right thoracotomy in the first stage and esophagogastrectomy through a subcutaneous route in the second stage. He reported esophagectomy under general anesthesia using the Melzer-Auer method. However, before the 2nd World War, general anesthesia was not always common in Japan, and resection of a cancer in the thoracic esophagus had extremely high mortality rates.4,5) After the 2nd World War, instruments and techniques for positive pressure ventilation under tracheal intubation were introduced in Japan and spread all over the country, so esophageal cancer surgery became possible in many major centers in Japan.5)
Here, we would like to present the historical developments in the concept of esophageal surgery in Japan, and a personal perspective on the future of esophageal surgery. We focused on surgery for locally-advanced T4 cancer of the thoracic esophagus. Concerning surgery for T4 cancer of the cervical esophagus, for that at the cervicothoracic junction, and for that at the esophagogastric junction, we would like to refer to other review articles.

The 1st Stage of Esophageal Surgery in Japan: Preoperative Radiotherapy Followed by Surgery

As shown in Table 1, during the 1st period from 1930 to 1980, several medical technologies such as general anesthesia with positive pressure ventilation under tracheal intubation, tube feeding, esophagography and others, were introduced in the treatment for esophageal cancer in Japan, and transthoracic esophagectomy for cancer spread all over the country. At that time, most esophageal cancers were at an advanced stage. Therefore, in order to increase resectability and to improve the prognosis, preoperative radiotherapy was initiated by Nakayama in Chiba University, followed by Akakura in Keio University, and others. In this period, the main concept of esophageal surgery was “safety”.

The 2nd Stage of Esophageal Surgery in Japan: Combined Resection of the Neighboring Organs with Esophagectomy for Cancer

In the 1970s and 1980s, medical technologies such as upper endoscopy using a flexible fiberscope, assisted ventilation, bronchial toiletting using a bronchoscope, nutritional support using intravenous hyperalimentation and parenteral nutrition, fluid control based on cardio-respiratory dymanics were introduced in the field of esophageal surgery (Table 1). An increase in potentially-resectable esophageal cancers and advances in perioperative management enhanced complete resection of an esophageal cancer. During the 2nd period from 1980 to 2000, extended surgery was attempted for esophageal cancers, involving combined resection of neighboring organs for T4 esophageal cancer and three-field lymphadenectomy for lymph node metastasis. The main concept of esophageal surgery in this period was “radicality”.

Surgical techniques of combined resection of the aorta and/or the trachea with esophagectomy were reported by several esophageal surgeons including Kawahara in the Industrial and Environmental Health School of Medicine, Ayabe in Nagasaki University, Kabuto in Osaka Medical Center for Cancer and Cardiovascular Diseases, and...
The 3rd Stage of Esophageal Surgery in Japan

Changing modality from radiotherapy to chemoradiotherapy raised question for resection of T4 esophageal cancers

Since 1990, many medical technologies such as microvascular anastomosis, endoscopic resection, thoracoscopic and laparoscopic surgery and others were introduced in the treatment of esophageal cancers. Around 2000, medical suits remarkably increased in Japan. The 3rd period of the Japanese esophageal surgery, an era of Quality of Life, developed since 2000. In this period, less invasive therapies such as functional preserving surgery, thoracoscopic and laparoscopic surgery, endoscopic resection, definitive chemoradiotherapy and others have become the mainstay for treating esophageal cancers (Table 1).

In 1980s, radiotherapy with or without surgery was most common for T4 esophageal cancers, while chemoradiotherapy for such cancers was not common in Japan. At that time, many esophageal surgeons believed that even palliative esophagectomy with perioperative chemotherapy and/or radiotherapy was superior to chemotherapy and/or radiotherapy without resection of T4 esophageal cancers.14–16 Retrospective studies frequently showed that the survival after surgery was superior to that after non-surgical treatment. However, surgery was commonly performed for T4 esophageal cancers slightly involving neighboring organs, while non-surgical treatments were commonly performed for those involving more severely neighboring organs. Moreover, only patients with the medically fit condition underwent surgery, while those with a medically unfit condition generally underwent non-surgical treatment. In 1987, we reported a retrospective study showing risk-adjusted survival curves in which the patient background was adjusted by multivariate analysis which showed no difference in the survival between esophagectomy and non-surgical treatment.17 The efficacy of surgery of T4 esophageal cancers even following or followed by radiotherapy was then raised as questionable.

On the other hand, already in 1981, Steiger, et al.18) in the United States reported that some combination of chemotherapy, radiotherapy and surgery provided excellent palliation and had a potential for cure, and they predicted a tri-modality treatment for esophageal cancer. Then in the 1990s, chemoradiotherapy was defined to be superior to radiotherapy-alone for esophageal cancers based on a randomized control trial.19) This concept was then introduced into treatment for T4 esophageal cancers.

In Japan, at that time, some esophageal surgeons considered that patients with an esophageal cancer would better tolerate surgery followed by (chemo)radiotherapy than preoperative (chemo)radiotherapy followed by esophagectomy.20) There was a controversy over which offered a benefit also for patients with a T4 esophageal cancer - neoadjuvant chemoradiotherapy versus adjuvant chemoradiotherapy. We therefore performed a prospective non-randomized trial comparing esophagectomy followed by chemoradiotherapy versus chemoradiotherapy followed by esophagectomy for unresectable T4 esophageal cancers, based on the patient's own choice after informed consent. In 2005, we reported the long-term result that chemoradiotherapy followed by esophagectomy offered a better survival compared to esophagectomy followed by chemoradiotherapy - being 19% vs. 0% for each 5-year survival rate.21) The additional multivariate analysis in this trial showed that the prognosis of patients with a T4 esophageal cancer was not related to esophagectomy, but to the efficacy of chemoradiotherapy. Thus the effect of “reduction surgery” for T4 esophageal cancers was defined as questionable.

In 1990s and 2000s, most esophageal surgeons considered that neo-adjuvant chemoradiotherapy followed by esophagectomy improved the survival of patients with a T4 esophageal cancers.22–25) They reported that patients whose resected specimen showed complete response (CR) to neo-adjuvant chemoradiotherapy had the best survival. They frequently emphasized that minute residual tumors were often observed in the resected specimens, and that CR and minute residual tumors could not be defined only by pathological examinations of the resected specimen.23) On the other hand, medical oncologists and radiation oncologists raised doubt over...
esophagectomy for complete responders. They initiated definitive chemoradiotherapy for esophageal cancers with a curative intent.

In 2000, Murakami, et al. reported a prospective trial showing that esophageal preservation could be achieved by additional definitive CRT for responders to neoadjuvant CRT in 39% of patients with a locally-advanced esophageal cancer. We also had started a prospective non-randomized trial comparing chemoradiotherapy with surgery versus without surgery for un-resectable T4 esophageal cancers. In 2005, we reported the results from this trial showing that surgery did not offer any survival benefit for responders to neo-adjuvant chemoradiotherapy, but might offer a survival benefit for non-responders. It seems that esophagectomy as salvage surgery was preferred only for non-responders to chemoradiotherapy for T4 esophageal cancers. At the same time, the result after two randomized control trials comparing neo-adjuvant chemoradiotherapy followed by surgery versus definitive chemoradiotherapy for locally-advanced T3T4 esophageal cancers were reported from Germany and France. Similarly to our result, both trials demonstrated no difference in the survival of responders to chemoradiotherapy between neo-adjuvant chemoradiotherapy followed by surgery and chemoradiotherapy-alone.

Although many surgical challenges have been done for T4 esophageal cancers, it is now considered that chemoradiotherapy is a standard treatment for un-resectable T4 esophageal cancers and that salvage surgery for residual tumor or recurrence may be an optional treatment for non-responders.

Salvage surgery after definitive chemoradiotherapy for T4 esophageal cancer

Salvage surgery is defined as surgery for residual tumor or recurrence after definitive chemoradiotherapy for esophageal cancers. Many reports concluded that salvage surgery was feasible, because there were long-term survivors after salvage surgery which were not obtained by other palliative treatments, although its post-operative mortality and morbidity rates were higher than those after planned surgery following neoadjuvant chemoradiotherapy. In the 10th edition of the Japanese Classification authorized by the Japan Esophageal Society published in 2008, salvage surgery is defined as surgery for residual or recurrence after definitive (chemo)radiotherapy in which radiotherapy more than 50 Gy is administered with curative intent for esophageal cancers. Then it is defined salvage surgery that incudes lymphadenectomy-alone and endoscopic resection, as well as esophagectomy.

In 2009, we reported the outcomes after treatment for residual tumors or recurrences after definitive chemoradiotherapy mainly for un-resectable T4 esophageal cancers. This retrospective study compared outcomes after salvage surgery with those after palliative treatments such as bypass operation, esophageal stenting, gastrostomy/jejunostomy and others. The 5-year-survival rate after salvage surgery was 13%, while all the patients who received palliative treatments died within 2 years. Next in 2010, we reported the result of a retrospective study analyzing prognostic factors of patients who underwent salvage esophagectomy. Incomplete resection (R1R2 resection), the presence of lymph node metastasis and non-responders to dCRT were correlated with a poor prognosis. The 5-year-survival rate after complete resection was 17%, while all the patients who underwent incomplete resection died within one year. Accordingly, when the residual tumor or recurrence after dCRT cannot be completely resected, then palliative treatments such as bypass operation are recommended rather than salvage esophagectomy, because resection of residual tumors after definitive chemoradiotherapy for a T4 esophageal cancer frequently results in being incomplete or impossible, and so, to surgeons’ regret, salvage surgery is rarely recommended for non-responders to dCRT.

New concept and techniques to treat T4 esophageal cancers

As cited above, the standard treatment for T4 esophageal cancer is dCRT. The efficacy of dCRT for such cancers is less than that for non-T4 tumors. At present, there are many patients with an esophageal cancer who have a residual tumor or recurrence involving the aorta and/or the trachea after dCRT. It is clear that incomplete resection of the tumor does not offer any benefit for those patients. Complete resection of the tumor, namely extended surgery, for such patients is expected to improve the survival of those. However, extended surgery such as salvage surgery is suspected to increase mortality and morbidity.

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. In 1987, we reported many types of tracheal repair using the latissimus dorsi muscle flap after resection of the trachea during esophagectomy for cancer. This procedure has been applied also for reinforcement of the tracheal membrane during salvage esophagectomy after dCRT.

When the tumor is suspected to involve the aorta, aortic stenting may be available for resection of the aorta affected by cancer. We performed an animal experiment on aortic stenting practicable for resection of the aorta during esophagectomy for cancer. In 2004, we reported that the canine aorta could be resected even immediately after aortic stenting, as well as 3 days after that. After such procedures, dogs could survive more than a year without any complication. In 2011, we reported three patients who underwent thoracic endovascular repair due to aortic complications including a fistula and an aneurysm after esophagectomy for cancer. Yamatsuji, et al. reported clinical cases in which aortic stenting was applied for esophagectomy for cancer. Those results suggested that an esophageal cancer involving the aorta might be resected by using new techniques such as aortic stenting even after dCRT.

Guidelines of treatment for T4 esophageal cancers

In the 2012 edition of the Guidelines for Diagnosis and Treatment of Carcinoma of the Esophagus authorized by the Japan Esophageal Society (JES), neoadjuvant CRT followed by surgery is recommended for unresectable T4 esophageal cancers, as well as dCRT or palliation. Surgery is, however, recommended only for resectable tumors resulted from down-staging following neoadjuvant CRT. Salvage surgery is not always recommended (Grade C1). The NCI PDQ Summary of Esophageal Cancer Treatment of Health Professionals 2012 reported in the US National Cancer Institute (NCI) internet homepage, and in the Esophageal Cancer Clinical Practice Guidelines published in the National Comprehensive Cancer Network (NCCN) 2011, that only dCRT with or without salvage surgery, or palliation is recommended for unresectable T4b esophageal cancers. Thus, the representative guidelines in the world do not always recommend surgery for unresectable T4 esophageal cancer. The reason seems to be that complete resection would be rarely possible for residual tumors or recurrences after dCRT for T4 tumors. Surgery, at present, plays a part of “Goal-keeper” in the treatment for T4 esophageal cancers. New surgical techniques for combined resection of the neighboring organs such as the aorta and/or the trachea with salvage esophagectomy may be needed to improve the survival of patients with a T4 esophageal cancer.

Summary and a Personal Perspective

The history of esophageal surgery in Japan can be divided into three periods, an era of safety from 1930 to 1980, an era of radicality from 1980 to 2000, and the era of QOL from 2000 to the present. The treatment for T4 esophageal cancers has also changed over time from preoperative radiotherapy, combined resection of the neighboring organs with esophagectomy, and to dCRT. At present, almost all patients with an unresectable T4 esophageal cancer receives dCRT. However, there are many patients with a residual or recurrent tumor after dCRT. Salvage surgery for such patients often results in incomplete resection of the tumor or being unresectable because the tumor involves the trachea and/or aorta. New techniques to enable the resection of the neighboring organs such as the trachea and/or aorta even during salvage surgery are needed.

In the future, the mainstay of treatment for esophageal cancer will be chemoradiotherapy with the foreseeable progress in new drugs and new techniques of radiotherapy. Surgery will be indicated for a local failure including...
an esophageal tumor and for metastasis in the regional lymph nodes after chemoradiotherapy (Fig. 1), while combined resection of the neighboring organs will be necessary to treat a local failure after chemoradiotherapy for T4 cancers. In order to achieve this purpose, new surgical techniques have to be developed through some application of new devices and equipment. On the other hand, chemoradiotherapy and surgery may be adopted also for patients having systemic disease to achieve better QOL through local control.

Disclosure Statement

The author has no conflicts of interest to declare.

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