Editorial

Salvage Surgery for Esophageal Carcinoma after Definitive Chemoradiation Therapy

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Introduction

The salvage operation for esophageal cancer is one of the most interesting topics today among Japanese doctors treating this form of malignant tumor. This topic has been selected as the focus of symposia and panel discussions at many annual meetings of surgical-, esophageal-, or digestive-disease–related societies in Japan. In parallel, definitive chemoradiation therapy has recently shown progress as a treatment modality for resectable esophageal cancer.[1–3] Many patients have chosen to undergo definitive chemoradiation therapy to preserve the upper digestive tract. However, definitive chemoradiation is not yet recognized as a standard therapy for resectable esophageal cancer, since no study has demonstrated better results than surgery. Late adverse events after definitive chemoradiation have been reported, and in failure cases of definitive chemoradiation, additional treatments, including salvage surgery, are often difficult.[4,5] Nevertheless, salvage treatment is needed to improve the overall treatment results in chemoradiation therapy.[3] The benefits and risks of salvage surgery are now a major theme of discussion.

Definitive Chemoradiation for Resectable Esophageal Cancer

Definitive chemoradiation therapy has recently been accepted as one of the important treatment modalities for resectable esophageal cancer. As a nonsurgical treatment, it yields superior results in comparison to radiation alone, based on a randomized controlled study performed by the Radiation Therapy Oncology Group. In the RTOG 85-01 trial, the 5- and 8-year survival rate of the chemoradiotherapy group was 27% and 22%, respectively.[1] Ishikura et al. have reported that the 5-year survival rate of definitive chemoradiotherapy for resectable cases was 49%. Chemoradiation, being a nonsurgical treatment, is a standard therapy for esophageal cancer based on the guidelines for esophageal cancer diagnosis and treatment in Japan. However, adverse events, especially those with a late onset, have been reported, including acute myocardial infarction, pericarditis, heart failure, pleural effusion, and radiation pneumonia. Furthermore, there have been some reports of the possibility of ischemic heart diseases being induced by radiation therapy.[6] These late adverse events have caused treatment-related deaths, even in complete response (CR) patients. These papers have concluded that definitive chemoradiation is effective, but that it comes with substantial toxicities. A comparison of the effects of high-dose (64.8 Gy) versus standard-dose (50.4 Gy) radiation therapy on the local control and toxicity revealed that a higher radiation dose did not increase the survival or local control.[2] Based on the results of a Phase III trial, the recommended radiation dose with concurrent 5-FU and cisplatin chemotherapy is 50.4 Gy. An additional investigation on minimizing normal tissue toxicities is warranted. There are still no data from randomized trials comparing definitive chemoradiation and surgery alone for the treatment of resectable esophageal cancer. These different modalities should be examined using a randomized control study, or, if impossible, a prospective clinical trial.

Chemoradiation Followed by Surgery

Surgery is the standard therapy for resectable esophageal cancer. In Japan, three-field lymph node dissection is available for squamous cell carcinoma of the thoracic esophagus. The outcome of the surgical treatment has been improved, but is not sufficient in all patients. Local recurrences after surgery are seen in R0 resection, and R2 resection cannot always be avoided in spite of improvement in preoperative diagnosis. From these points of view, preoperative treatment for resectable cancer has been investigated in many clinical studies. The theoretical benefits of preoperative treatment include improved resection

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rates, pathological downstaging, and a reduction in recurrence. The efficacy of neoadjuvant chemotherapy has been examined in two large-scale randomized control studies.[7,8] The results of these two studies were different. Therefore the usefulness of preoperative chemotherapy is still controversial. A meta-analysis of randomized controlled trials comparing neoadjuvant chemotherapy and surgery to surgery alone did not demonstrate a survival benefit for the combination of neoadjuvant chemotherapy and surgery.[9]

Preoperative chemoradiation is common, and it is also a widely used modality to improve the results of surgery. Many Phase III trials comparing chemoradiation followed by surgery and surgery alone did not show a benefit for preoperative chemoradiation.[10] Only Walsh et al. reported the efficacy of preoperative chemoradiation in improving the survival.[11] However, a meta-analysis of these trials revealed that chemoradiotherapy followed by surgery significantly reduced the 3-year mortality in comparison to surgery alone.[12] On the other hand, postoperative mortality was significantly increased by preoperative chemoradiation. One of the causes of these controversial results is that the mortality rate in the preoperative group was higher than that of the surgery-alone group. In our nonrandomized study, a three-field lymph node resection with preoperative chemoradiotherapy increased the morbidity rate, but did not increase operative death and in-hospital death in comparison to surgery alone.[13] We therefore need the results of a new large randomized control study with a low perioperative mortality.

In the comparative data between definitive chemoradiotherapy and chemoradiotherapy followed by surgery, chemoradiotherapy resulted in an equivalent survival rate in comparison to chemoradiation followed by surgery.[14] However, surgery significantly increased local control, and patients who underwent surgery had less chance of death from cancer. Moreover, the survival curves for overall survival seem to be different after 3 years. These conflicting findings should therefore be clarified in a large clinical trial.

Salvage Surgery after Definitive Chemoradiation

Definitive chemoradiation for resectable esophageal cancer is the standard therapy for nonresectable treatment as mentioned above. However, CR rates are about 70% in non-T4 disease. Local failure or local persistence has been observed with a higher rate in definitive chemoradiotherapy. Adams et al. have reported that patients who had chemoradiation had double the rate of local recurrence in comparison to those receiving surgery alone.[15] Ohtsu, an authority in chemoradiation for esophageal cancer in Japan, has mentioned that local failure has remained a major issue affecting 45% of patients in the chemoradiotherapy group.[3] Salvage surgery for unsuccessful curative chemoradiation improved the outcome of definitive chemoradiation treatment. However, these patients presented some difficulties during salvage surgery because they often had distant metastases or were in poor physical condition as a result of high-dose radiotherapy.

Salvage surgery is now considered to be an effective alternative surgical method. Neoadjuvant chemoradiotherapy has been shown to increase the morbidity and mortality associated with esophagectomy in many clinical trials, as mentioned above. Definitive chemoradiation has the possibility of further increasing the risks for esophagectomy.[16] A salvage esophagectomy is a high-risk surgical procedure because the patients are in poor physical condition. There are fibrous changes in the mediastinum after radiation, and there are difficulties of anastomosis as a result of the irradiated gastric tube. Respiratory failure and septic conditions resulting from a leakage of anastomosis are the major fatal complications. Urschel and Sellke reported acute respiratory distress syndrome and pneumonia causing respiratory failure after salvage esophagectomy.[17] An underlying radiation pneumonitis is probably the first insult to the lungs, and cytokine release during surgery is the second insult. Mechanical ventilation can cause lung injury, and pulmonary lymphatic obstructions also contribute to acute lung injury. Esophagogastric anastomotic leaks are caused by poor gastric tissue perfusion. Radiation of the proximal stomach can obliterate some of the rich plexus of submucosal vessels, and gastric tube necrosis, airway necrosis, and tracheogastric fistulae are also considered to be important complications. Swisher et al. mentioned that mechanical ventilation, intensive care unit stay, hospital stay, and the leakage of anastomosis are increased in patients undergoing salvage surgery after definitive chemoradiotherapy in comparison to those undergoing planned chemoradiation followed by surgery.[18] The operative mortality also increased in the salvage esophagectomy group. To reduce the complications of salvage esophagectomy, severe eligible criteria are needed. Nakamura et al. reported that there was no difference between the salvage group and the neoadjuvant chemoradiotherapy group in hospital mortality, mechanical ventilation, intensive care unit stay, and hospital

stay.[19] In our department, we have experienced no instances of 30-day hospital death, and salvage surgery is therefore not more morbid than a planned esophagectomy after chemoradiation. Most patients survived and were discharged, and they were also able to tolerate an oral diet. We have undergone esophagectomy with three-field lymph node dissection for salvage surgery. However, these patients were carefully selected because of the high operative risk, so this procedure has not been determined as a safe operation. The extent of lymph node dissection is still controversial.

Meunier et al. reported that the factors to predict prolonged survival times in cases of salvage surgery consist of the general health status, the type of initially resected tumor, and a certain recurrence-free delay.[20] Swisher et al. described the merits of salvage surgery in patients with early pathological stage, prolonged time to progression, and R0 resection.[18] A salvage operation remains a therapeutic option for carefully selected patients at experienced esophageal referral centers.

Salvage surgery for recurrent tumors after definitive chemoradiation is still being improved as an operative method. Issues on lymph node dissection, the criteria of patients' eligibility, and the period from recurrence to operation must be addressed. In the future we will attempt to determine whether salvage surgery or a planned esopohagectomy after chemoradiation is the better option.

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