Esophageal Bypass Operation Prior to Definitive Chemoradiotherapy in Advanced Esophageal Cancer With Tracheobronchial Invasion

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Background. In T4 esophageal cancer with tracheobronchial invasion, an esophagorespiratory fistula (ERF) often occurs during or after chemoradiotherapy. We have performed esophageal bypass operations prior to definitive chemoradiotherapy for these patients to increase the chemoradiotherapy completion rate by minimizing the potential effect of an ERF. The aim of this study was to examine the clinical outcome of esophageal bypass surgery prior to chemoradiotherapy.

Methods. Between 1997 and 2010, 17 patients underwent esophageal bypass surgery followed by definitive chemoradiotherapy for esophageal cancer with tracheobronchial invasion (bypass group). Ten patients in the same circumstances were treated with chemoradiotherapy alone (control group). Overall survival, the clinical effect of chemoradiotherapy, the ERF incidence rate, and the safety of esophageal bypass surgery were assessed.

Results. The overall response rate to chemoradiotherapy was 64.7% in the bypass group and 90.0% in the control group. Except for 2 patients with ERF at initial diagnosis, 4 (26.7%) of the 15 patients developed ERF in the bypass group, and 3 (30.0%) of the 10 patients developed ERF in the control group during or after chemoradiotherapy. The 2-year and 3-year overall survival rates were 17.6% and 17.6% in the bypass group and 20.0% and 0% in the control group, respectively (p = 0.924); long-term survival of more than 3 years was seen only in the bypass group.

Conclusions. Esophageal bypass surgery prior to definitive chemoradiotherapy could be performed safely, and this strategy contributed to long-term survival in the patients who achieved a good response to chemoradiotherapy but developed an ERF.

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are in good condition to reduce potential postoperative complications and to complete CRT even if ERF occurs during CRT. In this report, 17 esophageal cancer patients with tracheobronchial invasion who underwent esophageal bypass surgery followed by CRT were reviewed and analyzed, and their results were compared with those of patients in the same circumstances who did not undergo bypass surgery during the same time frame.

**Patients and Methods**

**Patients**

Twenty-seven locally advanced esophageal cancer patients with tracheobronchial invasion between 1997 and 2010 in Hiroshima University Hospital were studied. Most patients had squamous cell carcinoma, except for 1 patient with carcinosarcoma of the esophagus. Seventeen patients underwent esophageal bypass surgery followed by definitive CRT (bypass group). The criteria for esophageal bypass surgery required the following: (1) clinically evident tracheobronchial invasion; (2) good organ function and ECOG [Eastern Cooperative Oncology Group] performance status 0 or 1; (3) no recurrent laryngeal nerve paralysis; (4) no cervical lymph node metastases; (5) no distant organ metastases and pleural dissemination; and (6) agreed with surgery. Another 10 patients did not undergo esophageal bypass surgery and immediately began definitive CRT (control group). All patients in the control group were ECOG performance status 0 or 1 with good organ function and showed no evidence of distant organ metastases and pleural dissemination. Reasons for avoiding esophageal bypass surgery were cervical node metastases in 3 patients and did not agree with surgery in 7. The patients’ and their tumors’ characteristics in both groups are shown in Table 1. The clinical tumor staging was defined according to the 6th TNM classification of the International Union Against Cancer [19]. Most patients had dysphagia caused by advanced primary esophageal tumor. Twenty-six patients had squamous cell carcinoma and 1 in the bypass group had carcinosarcoma. The majority of tumors were located astride the upper and middle third of the esophagus, while tumor center was located more frequently in the middle third in the bypass group (p < 0.001). Most patients were stage T4N0-1M0, while 1 in the bypass group had metastasis in the gastric wall (T4N1M1b) and 3 in the control group had cervical node metastasis (T4N1M1a). Airway invasion was predominantly in the left main bronchus in the bypass group and in the trachea in the control group (p = 0.005). Every patient had an esophagoscopy and computed tomography scan of the neck, thorax, and abdomen for staging. Tracheobronchial invasion was diagnosed by computed tomography scan and bronchoscopy. Two patients in the bypass group and 4 patients in the

**Table 1. Patients’ Clinical Characteristics**

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>Bypass Group (n = 17) n (%)</th>
<th>Control Group (n = 10) n (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>0.269</td>
</tr>
<tr>
<td>Male</td>
<td>16 (94.1)</td>
<td>8 (80.0)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1 (5.9)</td>
<td>2 (20.0)</td>
<td></td>
</tr>
<tr>
<td>Age, mean [range]</td>
<td>62.9 (51–77)</td>
<td>68.9 (58–81)</td>
<td>0.109</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysphagia</td>
<td>16 (94.1)</td>
<td>8 (80.0)</td>
<td>0.269</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>2 (11.8)</td>
<td>0 (0.0)</td>
<td>0.060</td>
</tr>
<tr>
<td>Chest pain</td>
<td>2 (11.8)</td>
<td>0 (0.0)</td>
<td>0.060</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>1 (5.9)</td>
<td>1 (10.0)</td>
<td>0.699</td>
</tr>
<tr>
<td>Histopathologic cell type</td>
<td></td>
<td></td>
<td>0.443</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>16 (94.1)</td>
<td>10 (100)</td>
<td></td>
</tr>
<tr>
<td>Carcinosarcoma</td>
<td>1 (5.9)</td>
<td>0 (0.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Main tumor site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper third</td>
<td>3 (17.6)</td>
<td>9 (90.0)</td>
<td></td>
</tr>
<tr>
<td>Middle third</td>
<td>14 (82.4)</td>
<td>1 (10.0)</td>
<td></td>
</tr>
<tr>
<td>Tumor length (mm), mean [range]</td>
<td>77 (40–120)</td>
<td>67 (50–100)</td>
<td>0.204</td>
</tr>
<tr>
<td>Clinical TNM stage</td>
<td></td>
<td></td>
<td>0.133</td>
</tr>
<tr>
<td>T4N0M0</td>
<td>4 (23.5)</td>
<td>1 (10.0)</td>
<td></td>
</tr>
<tr>
<td>T4N1M0</td>
<td>12 (70.6)</td>
<td>6 (60.0)</td>
<td></td>
</tr>
<tr>
<td>T4N1M1a</td>
<td>0 (0.0)</td>
<td>3 (30.0)</td>
<td></td>
</tr>
<tr>
<td>T4N1M1b</td>
<td>1 (5.9)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Site of airway invasion:</td>
<td></td>
<td></td>
<td>0.005</td>
</tr>
<tr>
<td>Left main bronchus</td>
<td>14 (82.4)</td>
<td>2 (20.0)</td>
<td></td>
</tr>
<tr>
<td>Trachea</td>
<td>3 (17.6)</td>
<td>8 (80.0)</td>
<td></td>
</tr>
</tbody>
</table>
control group had invasion of the descending aorta along with tracheobronchial invasion. In the bypass group, 2 had a symptomatic esophagobronchial fistula at initial diagnosis. We obtained appropriate approval for this study from the Institutional Review Board of Hiroshima University Hospital.

**Esophageal Bypass Surgery**

All patients underwent esophageal bypass surgery prior to CRT. Surgery was performed according to the procedure we previously reported [20]. With the patient in the supine position, an upper midline abdominal incision was made. A wide gastric tube from the greater curvature or a whole stomach tube was prepared for reconstruction with finger pyloroplasty. The abdominal esophagus was divided, and a polyethylene tube was inserted into the esophagus and fixed by a running suture with absorbable surgical suture (Fig 1). The distal side of the polyethylene tube was brought out from the left hypochondrial region as a tube esophagostomy. Next, an incision was made in the left side of the neck, and the cervical esophagus was divided above the sternal notch. The esophageal stump was closed by hand-sewing or a linear stapler. The gastric tube was then pulled up through the retrosternal route to the neck and anastomosed to the cervical esophagus. Anastomosis was performed using the hand-sewing technique in 16 patients and the triangulating stapling technique [21] in 1. Drainage tubes were placed around the cervical anastomosis and in the left subphrenic space. A narrow (12- or 14-Fr) drainage tube was inserted retrogradely through the tube esophagostomy into the remnant esophagus, and the tip of the narrow drainage tube was placed between the oral esophageal stump and the primary tumor to decompress and avoid rupture at the stump (Fig 1).

**Postoperative Management**

All patients were extubated immediately after surgery in the operating room and managed on a general surgical ward. Oral intake was started after assessment of the esophagogastric anastomosis and swallowing ability with water-soluble contrast on postoperative day (POD) 7 to 10. The polyethylene esophagostomy tube was removed on POD 14 to 21 when the esophageal-skin fistula formed, while the narrow drainage tube was still indwelled permanently. This narrow drainage tube was changed monthly.

**Chemoradiotherapy**

In the bypass group, patients received definitive CRT at least 13 days after esophageal bypass surgery. In both groups, fractionated radiotherapy was performed with a total dose of 50 to 66 GY delivered in 1.8 to 2.0 Gy per fraction. Chemotherapy protocols administered concomitantly with radiation were daily low-dose CDDP and 5-FU (low-dose CF), standard-dose CDDP and 5-FU (standard CF), or weekly docetaxel (DOC) and daily 5-FU (DF). In the low-dose CF protocol, CDDP 3 mg/m² per hour and 5-FU 250 mg/m² every 24 hours were given on each day of radiation. The standard CF protocol consisted of 2 courses of chemotherapy (CDDP 70 mg/m² on day 1 with 5-FU 700 mg/m² every 24 hours on days 1 to 4, q28 days). In the DF protocol, DOC 7.5 mg/m² was given on days 1, 8, 22, and 29, and 5-FU 250 mg/m² every 24 hours was administered on each day of radiation according to our phase I protocol [22]. The clinical response was evaluated on the basis of the Response Evaluation Criteria in Solid Tumors [23].

**Statistics**

Overall survival (OS) was defined as the time interval between the date of surgery and documentation of the day of death or last follow-up in the bypass group, and between the starting date of the chemoradiotherapy and documentation of the day of death or last follow-up in the control group. The OS was calculated according to the Kaplan-Meier method and compared using the log-rank test. Groups were compared using t tests or Mann-Whitney tests. A p value less than 0.05 was considered significant. Data analysis was performed using SPSS software (version 20.0; IBM Corporation, Armonk, NY).

**Results**

**Surgical Outcome of Esophageal Bypass Surgery**

The median operation time was 210 (range 170 to 275) minutes, and median blood loss was 220 g (range 50 to 580). Postoperative complications were anastomotic leakage (n = 2; 11.8%), recurrent laryngeal nerve paralysis (n = 2; 11.8%), pneumonia (n = 2; 11.8%), abdominal abscess (n = 2; 11.8%), and torsion of the gastric tube (n = 1; 5.9%). There was no 30-day mortality (Table 2). Two
patients with an anastomotic leakage were able to resume oral nutrition at POD 23 and 58, respectively. An abdominal abscess arose at the left subphrenic space due to leakage of esophageal discharge from the junction of the abdominal esophagus and the polyethylene esophagostomy tube. The abscess was well drained through the left subphrenic drainage tube and disappeared in 2 weeks. Reoperation was needed to repair torsion of the gastric tube.

Oral intake could be resumed after a median of 9 (range 7 to 58) days postoperatively. Of the 17 patients, 14 were able to resume normal oral food intake, and 3 were able to take liquids only. These 3 patients all had progressive disease with appearance of distant metastases, and their performance status deteriorated progressively. The other 14 patients could take normal food during CRT after bypass surgery and were free from symptoms of esophageal stricture and esophagitis.

Effect of Chemoradiotherapy
In the bypass group, patients could begin definitive CRT on POD 13 to 43 (median POD 17) after esophageal bypass surgery. In 3 cases, CRT began more than 30 days after surgery, and the reasons for the delay were postoperative complications (anastomotic leakage, abdominal abscess, and torsion of the gastric tube). The effects of CRT in both groups are summarized in Table 3. The overall response rate to CRT was 64.7% (11 of 17) in the bypass group and 90.0% (9 of 10) in the control group.

Except for 2 cases with ERF at initial diagnosis, 4 (26.7%) of the 15 patients developed ERF during or after CRT in the bypass group. Esophageal bypass surgery before CRT allowed them to continue oral intake and avoid severe respiratory symptoms. On the other hand, 3 (30.0%) of the 10 patients developed ERF in the control group. The ERF occurred during CRT in 1 patient and after CRT in 2, and all 10 patients completed CRT. Two patients underwent esophageal stenting, and 1 needed both esophageal and bronchial stenting to occlude the ERF. They resumed oral intake temporarily, but 2 patients died due to bleeding after 7 and 62 days, respectively, and 1 died due to cancer progression 10 days after stent placement.

Survival
The overall 2-year survival, 3-year survival, and median survival time were 17.6%, 17.6%, and 9.7 months in the bypass group and 20.0%, 0%, and 8.7 months in the control group, respectively (Fig 2). There was no significant difference in survival between the 2 groups (p = 0.924), whereas long-term survival of more than 3 years was seen only in the esophageal bypass group. These 3 patients could consume normal food and lead a normal life.

Comment
In T4 esophageal cancer with tracheobronchial invasion, ERF occurs frequently during or after CRT. In our 15 bypass group patients, excluding 2 patients with ERF at initial diagnosis, ERF occurred in 4 patients (26.7%) during or after CRT, but they all continued normal food intake and completed CRT with no or minimal respiratory symptoms because the respiratory and alimentary tracts had been divided by prior bypass surgery. On the other hand, 3 (30.0%) of 10 patients developed ERF in the control group. The incidence of ERF related to CRT in both groups was in accordance with the previous reports [6-8] and did not differ by esophageal bypass surgery status.

Recently, ERF has usually been treated palliatively by esophageal stent, tracheobronchial stent, or their combination. However, the clinical results of these stent therapies have been unsatisfactory. Most patients are allowed to consume orally no more than semisolid food, and a high incidence of recurrent fistula, enlargement of the fistula due to pressure from the stents, and some life-threatening early complications have also been reported [9-12]. An ERF was treated with esophageal or both esophageal and bronchial stenting for 3 patients in the
control group, but oral intake was temporary, and 2 patients died due to sudden bleeding.

We have performed esophageal bypass surgery prior to definitive CRT while the patients are in good condition to reduce potential postoperative complications. This procedure required a median operation time of 210 minutes, with a median blood loss of 220 g, and these results were considered to be minimally invasive. Regarding postoperative complications, the frequency of postoperative complications was considered acceptable. There was no mortality at 1 month, and 2 patients died in hospital due to cancer progression (53 and 193 days).

With regard to the surgical procedure, the stomach and colon have been used as a conduit for reconstruction in esophageal bypass surgery [20, 24–26]. When the stomach is used as a conduit for reconstruction, drainage of secretions from the remnant esophagus is a concern. In this regard, internal esophageal drainage [26, 27] and external esophageal drainage [20, 24] have been reported. We created a tube esophagostomy for external esophageal drainage because our indication for this surgery was limited to patients with tracheobronchial invasion, and internal esophageal drainage such as an esophagojunostomy was associated with the danger of aspirating digestive fluids when ERF developed.

The prognosis of T4 esophageal cancer is generally poor, but 5-year survival of 7% to 14% is expected after definitive CRT [1–6]. The completion of CRT is considered to be one of the most important factors for a favorable outcome in these patients. Preceding esophageal bypass surgery may contribute to increasing the completion rate of subsequent definitive CRT without interruption of therapy even if an ERF develops during CRT in esophageal cancer patients with tracheobronchial invasion. In the bypass group, all 4 patients who developed ERF completed their treatment with minimal respiratory symptoms. Although there was no significant difference in survival between the bypass group and the control group, long-term survival of more than 3 years was seen only in the bypass group. In the previous reports, long-term survival of more than 3 years was not demonstrated in patients with ERF treated by stent therapy because of cancer progression and complications of stent insertion [10–12, 28, 29]. Thus, esophageal bypass surgery did not directly improve the response to CRT, though in patients who achieve a good response to CRT but develop an ERF, long-term survival can be expected with esophageal bypass surgery, but not with stent therapy.

There were some limitations to this study. It was not a prospective or randomized study, and the number of patients was small because patients with tracheobronchial invasion without distant organ metastasis are relatively rare. There was an imbalance in stage distribution between the bypass group and the control group because of the inclusion of 3 patients with cervical node metastasis (M1a) in the control group. In the Japanese Classification of Esophageal Cancer [30], cervical paraesophageal and supraclavicular nodes are regarded as regional nodes, and these 3 patients’ metastatic cervical nodes were limited to these lymph nodes. When the 3 patients with cervical node metastasis were excluded from the control group, the overall 2-year and 3-year survivals and median survival time were 28.6%, 0%, and 7.7 months, respectively. Because there was no significant difference in survival compared with the bypass group (p = 0.7974), we consider that the effect of stage imbalance on the clinical results was minimal.

Fig 2. Overall survival rates of the bypass group and the control group. The 2-year and 3-year overall survival rates and the median survival time (MST) were 17.6%, 17.6%, and 9.7 months in the bypass group and 20.0%, 0%, and 8.7 months in the control group, respectively (p = 0.924). Long-term survival of more than 3 years was seen only in the bypass group.
There are also some controversies with respect to this strategy. First, preceding bypass surgery delays the start of chemoradiotherapy. The clinical effect of CRT was better in the control group (90.0% vs 64.7%), and the delay of CRT seemed to affect this result. However, there was no significant difference in survival, and the negative effect of the delay was considered minimal. Second, esophageal bypass surgery might be unnecessary for 70% of patients in the bypass group because they did not eventually develop an ERF. The indications for esophageal bypass surgery can be limited if more accurate methods to predict ERF before CRT are developed. To that end, we are planning to limit the application of prophylactic bypass surgery to patients with obvious findings of airway invasion; eg, redness or ulceration on bronchoscopy. Simultaneously, the direction of the tumor ulcer floor (to the membranous portion of the airway or not) should be considered. Third, esophageal bypass surgery precludes oral endoscopic examination of the remnant esophagus, and it may be difficult to make a diagnosis of complete response, relapse of the primary lesion, and second primary esophageal cancer. In this regard, positron emission tomography–CT is helpful for diagnosis, and examination through esophagostomy using a thin fibrescope may be possible.

In conclusion, esophageal bypass surgery prior to definitive CRT could be performed safely when limited to appropriate cases, and it contributed to long-term survival in patients who achieved a good response to CRT but developed an ERF. In the future, the complete response rate will be increased by CRT using new agents such as molecular targeting drugs, and the usefulness of this strategy will increase.

References