Preoperative Chemoradiotherapy for Esophageal Cancer: Factors Associated with Clinical Response and Postoperative Complications

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Abstract. Background: The factors associated with the clinical results of preoperative chemoradiotherapy (CRT) for esophageal cancer and its effect on postoperative complications are still unclear. Patients and Methods: The 686 patients with esophageal cancer were classified into 376 who received preoperative CRT (group I) and 310 who received surgery alone (group II). Results: A multivariate analysis for group I patients revealed pathologically complete response to be a favorable prognostic factor. Preoperative use of cisplatin was significantly associated with pathological effect and patients’ prognosis. Both pulmonary complications and anastomotic leakage more frequently developed in group I (16.0 and 27.9%) than in group II (10.0%, p<0.05 and 16.5%, p<0.01, respectively). A multivariate analysis revealed preoperative CRT to be an independent factor of postoperative complications. Conclusion: Although preoperative CRT for esophageal cancer may be associated with postoperative complications, a pathologically complete response, which is associated with a cisplatin-based regimen, is critical for improving patient prognosis.

Esophageal cancer is fairly aggressive with poor prognosis and the 5-year survival had been reported to be 10 to 20% (1, 2). Recently, the 5-year survival rate after an esophagectomy has improved to 40-50% in high-volume centers in Japan and Western countries due to multifactorial factors, such as increase in the detection of early-stage cancer, accurate preoperative staging and improvement of surgical techniques as well as perioperative management (3-6). The systematic reviews from the MD Anderson Cancer Center emphasize that the increased use of preoperative chemoradiotherapy (CRT) may have contributed to the observed increase in survival after an esophagectomy (7).

A combination of chemotherapy and/or radiation can be applied preoperatively or postoperatively. Preoperative CRT has been applied for esophageal cancer, mainly at the advanced stage, for the purpose of down-staging and control of microscopic metastasis. However, the clinical efficacy still remains controversial: Some randomized studies emphasize the superiority of the clinical results in preoperative CRT plus surgery to the surgery alone group (8-10). However, others reported the difference not to be significant (11-13). Furthermore, some authors have reported that preoperative CRT for esophageal cancer increases the incidence of postoperative complications after an esophagectomy (8, 14, 15) although others reported the incidence of complications to be similar to that without preoperative therapy (16-18).

In order to avoid the complications associated with preoperative CRT, it is important to determine the appropriate indications of CRT by clarifying the factors associated with good clinical results. A pathologically complete response is reported to be important for long-term survival after an esophagectomy (19-22). However, the factors associated with a pathologically complete response are still unclear. This study evaluated the factors associated with the clinical response as well as those with the prognosis based on a multivariate analysis. Furthermore, the relationship between preoperative CRT and the development of postoperative complications was examined.

Patients and Methods

Patients. Eight hundred and seventeen patients with squamous cell carcinoma of the esophagus underwent an esophagectomy between 1980 and 2007, at the Department of Surgery and Science (Department of Surgery II), Kyushu University Hospital in Japan. Among these patients, preoperative radiotherapy without chemotherapy was administered to 86 patients, while preoperative...
Chemotherapy without radiotherapy was indicated for 25 patients. On the other hand, 20 patients underwent a salvage esophagectomy for residual or recurrent esophageal cancer after definitive chemoradiotherapy (radiation dose of 50 Gy or more). Excluding these patients, the subjects of this study were 686 Japanese patients. There were 595 men and 91 women, with a mean age of 63.3 years (range, 36 to 90 years). The survival data were updated in December 2008. The follow-up ranged from 13 days to 23 years after the primary operation (median follow-up period of censored patients, 3.9 years) and data were available for all patients.

The patients were divided into two groups according to the preoperative treatment: group I included 367 patients who underwent preoperative chemoradiotherapy; group II had 310 patients who underwent an esophagectomy without preoperative radiotherapy or chemotherapy. There were some differences in the clinical backgrounds between these two groups: The incidence of T3/T4 tumors was significantly higher in the preoperative CRT group (group I) than in the surgery alone group (group II). The retrosternal or subcutaneous route for reconstruction was more frequently indicated in group I than in group II patients (p<0.01). Furthermore, the indication for surgery alone (group II) significantly increased after 1994 (p<0.01). However, no differences were observed in factors, such as age, gender, location of the tumor lymph node metastasis, extent of lymphadenectomy and the organ used for reconstruction (Table I).

For all patients in group I, 30-42 Gy of radiation was administered preoperatively. Regarding chemotherapy, regimens without platinum, mainly a bleomycin-based regimen, were used for 189 patients before 1991, while both cisplatin and 5-fluorouracil were administered to 187 patients after 1992. For 204 patients, preoperative hyperthermia (42.5°C, 30 min, 6 times) was also applied using a radiofrequency system with an endotract electrode (Endoradiotherm 100A; Olympus Co, Tokyo, Japan) as previously reported (23).

### Table I. Clinical backgrounds of each group according to the preoperative chemoradiotherapy.

<table>
<thead>
<tr>
<th>Clinical factors</th>
<th>Preoperative therapy</th>
<th>Group I (Preoperative CRT)</th>
<th>Group II (Surgery alone)</th>
<th>Total n=686</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age: Mean±S.D. (years)</strong></td>
<td></td>
<td>62.8±9.3</td>
<td>64.0±9.7</td>
<td>63.3±9.4</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td>322 (85.6)</td>
<td>273 (88.1)</td>
<td>595 (86.7)</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td>54 (14.4)</td>
<td>37 (11.9)</td>
<td>91 (13.3)</td>
</tr>
<tr>
<td><strong>Location of the tumor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper esophagus</td>
<td></td>
<td>68 (18.1)</td>
<td>32 (10.3)</td>
<td>100 (14.6)</td>
</tr>
<tr>
<td>Mid-esophagus</td>
<td></td>
<td>218 (58.0)</td>
<td>166 (53.5)</td>
<td>384 (56.0)</td>
</tr>
<tr>
<td>Lower esophagus</td>
<td></td>
<td>90 (23.9)</td>
<td>112 (36.1)</td>
<td>202 (29.4)</td>
</tr>
<tr>
<td><strong>Depth of invasion</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1, 2</td>
<td></td>
<td>109 (29.0)</td>
<td>185 (59.7)</td>
<td>294 (42.9)</td>
</tr>
<tr>
<td>T3, 4</td>
<td></td>
<td>267 (71.0)*</td>
<td>125 (40.3)*</td>
<td>392 (57.1)</td>
</tr>
<tr>
<td><strong>Lymph node metastasis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td></td>
<td>197 (52.4)</td>
<td>178 (57.4)</td>
<td>375 (54.7)</td>
</tr>
<tr>
<td>Positive</td>
<td></td>
<td>179 (47.6)</td>
<td>132 (42.6)</td>
<td>311 (45.3)</td>
</tr>
<tr>
<td><strong>Extent of lymphadenectomy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Two-field</td>
<td></td>
<td>297 (79.0)</td>
<td>230 (74.2)</td>
<td>527 (76.8)</td>
</tr>
<tr>
<td>Three-field</td>
<td></td>
<td>79 (21.0)</td>
<td>80 (25.8)</td>
<td>159 (23.2)</td>
</tr>
<tr>
<td><strong>Organ used for reconstruction</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastric tube</td>
<td></td>
<td>333 (88.6)</td>
<td>273 (88.1)</td>
<td>606 (88.3)</td>
</tr>
<tr>
<td>Colon</td>
<td></td>
<td>25 (6.6)</td>
<td>21 (6.8)</td>
<td>46 (6.7)</td>
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<tr>
<td>Jejunum</td>
<td></td>
<td>13 (3.5)</td>
<td>13 (4.2)</td>
<td>26 (3.8)</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>5 (1.3)</td>
<td>3 (1.0)</td>
<td>8 (1.2)</td>
</tr>
<tr>
<td><strong>Route of reconstruction</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retrosternal / subcutaneous</td>
<td></td>
<td>260 (69.1)</td>
<td>130 (41.9)</td>
<td>390 (56.9)</td>
</tr>
<tr>
<td>Intramediastinal / posterior mediastinum</td>
<td></td>
<td>104 (27.7)*</td>
<td>167 (53.9)*</td>
<td>271 (39.5)</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>12 (3.2)</td>
<td>13 (4.2)</td>
<td>25 (3.6)</td>
</tr>
<tr>
<td><strong>Period of surgery</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1980-1993</td>
<td></td>
<td>233 (62.0)</td>
<td>123 (39.7)</td>
<td>356 (51.9)</td>
</tr>
<tr>
<td>1994-2007</td>
<td></td>
<td>143 (38.0)*</td>
<td>187 (60.3)*</td>
<td>330 (48.1)</td>
</tr>
</tbody>
</table>

*p<0.01 by Fisher’s exact test between Group I and II.

### Staging of the tumor and histological effectiveness of preoperative chemoradiotherapy.

The clinicopathological factors were evaluated according to the guidelines for clinical and pathological studies on carcinoma of the esophagus. The staging of the tumor was based on the TNM classification defined by UICC (24). The effects of preoperative chemoradiotherapy were evaluated according to the histopathological criteria for the effects of radiation and/or...
anticancer chemotherapy in the Guidelines for the Clinical and Pathological Studies on Carcinoma of the Esophagus established by the Japanese Society for Esophageal Diseases (25). Grade 0: Ineffective, there is no discernible therapeutic effect on the cancer tissue or cells. Grade 1: Slightly effective, apparently viable cancer cells account for 1/3 or more of the tumor tissue, but there is some evidence of degeneration of the cancer tissue or cells. Grade 2: Moderately effective, viable cancer cells account for less than 1/3 of the tumor tissue, while the other cancer cells are severely degenerated or necrotic. Grade 3: Markedly effective, no viable cancer cells are evident, and it is consistent with a pathologically complete response.

Statistical analysis. The differences in the distribution frequencies among the groups were evaluated using Fisher’s exact test or unpaired t-test. The independent factors associated with effectiveness for preoperative CRT as well as postoperative complications were evaluated with the logistic regression analysis. The survival curves were plotted according to the Kaplan-Meier method and any differences between the two curves were analyzed using the log-rank test (26). Trends in survival across ordered groups were tested using the trend log-rank test. A multivariate analysis with the Cox proportional hazard model was adopted to clarify the independent prognostic factors. Differences were considered to be significant if the p-value was less than 0.05. Data were analyzed using the StatView software package (Abacus Concepts, Inc., Berkeley, CA, USA).

Results

Clinical results of preoperative chemoradiotherapy in 376 patients with esophageal cancer. Among the 376 patients who received preoperative chemoradiotherapy, a grade 3 (markedly effective, pathologically complete response) and grade 2 (moderately effective) histological effect was observed in 67 patients (17.8%) and 151 patients (40.1%), respectively. In the other 158 patients, the histological effects of preoperative CRT were grade 0 (not effective) or grade 1 (slightly effective).

Figure 1 indicates the overall survival after the operation according to the histological effectiveness of preoperative chemoradiotherapy in patients with esophageal cancer who underwent preoperative CRT. Each Grade indicates the histological effectiveness: (Grade 0, 1: ineffective or slightly effective; Grade 2: moderately effective; and Grade 3: markedly effective). The survival of patients in whom preoperative CRT was markedly effective (grade 3) was significantly better than patients whose histological effect was moderately effective (grade 2), or not effective (grade 0 or 1, p<0.01).

Table II shows the independent factors associated with cancer recurrence including the histological effectiveness of preoperative CRT by an analysis according to the Cox proportional hazard model. As a result, not only lymph node metastasis, the resectability of the tumor and the period of surgery, but also the effectiveness of preoperative CRT were significant factors associated with cancer recurrence. The hazard ratio of cancer recurrence in patients showing a grade 3 histological effect was 0.33 (95% CI: 0.20-0.54) in comparison with patients with grade 0 or 1 effect.

Table III indicates the independent factors associated with a markedly effective histological response (grade 3) for preoperative CRT based on a logistic regression analysis. The favorable significant factors were a T1/T2 tumor, preoperative administration of cisplatin and hyperthermic therapy combined with preoperative CRT. The hazard ratios were 1.77 (95% Cl: 1.02-3.08) and 1.86 (1.02-3.37) for cisplatin and hyperthermia, respectively.
Figure 2 shows the overall survival of 187 patients who received intravenous administration of cisplatin as preoperative CRT and that of 189 patients who received preoperative CRT without cisplatin. The overall survival in patients with a cisplatin regimen was significantly better than those without cisplatin: the 5-year survival rates were 42.2% and 17.5% ($p<0.01$). Regarding preoperative hyperthermia, the 5-year survival rate was 36.4% and 29.0% in patients with and without hyperthermia, respectively, although the difference was not significant. A multivariate analysis also revealed the preoperative use of cisplatin as well as lymph node metastasis and resectability to be independent factors...
associated with cancer recurrence. The hazard ratio of cancer recurrence in patients with preoperative administration of cisplatin was 0.62 (95% CI: 0.39-1.00) in comparison to those without cisplatin (Table IV).

Preoperative CRT and postoperative complication. Table V shows the postoperative complications and hospital mortality of each group according to the use of preoperative chemoradiotherapy. Table VI shows the independent factors associated with the development of postoperative complications by a logistic regression analysis. Among the clinical factors, preoperative radiotherapy as well as the route of reconstruction were significant independent factors associated with complications: The odds ratio of patients who received preoperative CRT was 1.64 (95% C.I.: 1.13-2.38) in comparison to the surgery alone group, while it was 2.26 (1.48-3.45) for the subcutaneous or retrosternal reconstruction-route, in comparison to either the posterior mediastinum or intrathoracic route.

Discussion

For the locoregional treatment of esophageal cancer, there is some evidence to support combined chemoradiotherapy over radiotherapy alone (27). Preoperative cisplatin-based CRT is a useful tool for down-staging as well as prolonging long-term survival in patients with squamous cell carcinoma of
the esophagus (28). However, the effect of preoperative CRT on long-term survival remains controversial. Several meta-analysis studies have been reported to resolve this problem. Gebkski et al. (9) revealed that the all-cause mortality with neoadjuvant CRT versus surgery alone was 0.81 (95% CI: 0.70-0.93) with similar results for different histological types: 0.84 (0.71-0.99) for SCC and 0.75 (0.59-0.95). Fiorica et al. (10) also reported that preoperative CRT plus surgery in comparison with surgery alone reduced the three year mortality rate with an OR of 0.53 (0.31-0.93). On the other hand, Greer et al. (13) reported preoperative CRT to be associated with a small, non-statistically significant improvement in overall survival (OR: 0.86, 95% CI: 0.74-1.01). These meta-analytical studies support the survival benefits of preoperative CRT for esophageal cancer, although there are some differences in the OR probably due to differences in the collection of randomized control studies.

In terms of the long-term survival after CRT followed by surgery for esophageal cancer, the response for preoperative CRT is the most important factor: Pathologically complete response (no residual cancer cell) is considered to be especially important (19-22). Furthermore, Swisher et al. (21) emphasized that the pathological response is an independent risk factor for survival and proposed a revision of the esophageal cancer staging system to accommodate pathological responses following preoperative CRT. The current study also revealed the prognosis of the patients showing a pathologically complete response to be significantly better than other groups and a multivariate analysis revealed that a pathologically complete response is an independent favorable prognostic factor after a resection following preoperative CRT.

A multivariate analysis was performed in order to clarify the clinical factors associated with a pathologically complete response. The depth of invasion was found to be one of the independent factors associated with a clinical response for CRT and the presence of adventitial invasion was an unfavorable factor. This must be due to multiple factors such as the fact that an advanced tumor not only has a large tumor volume but also intra-tumoral heterogeneity and that, especially in the central part of the advanced tumors, radiation is not effective due to hypoxic conditions and it is difficult for chemotherapeutic agents to reach these areas due to a poor blood flow.

Administration of cisplatin and intraluminal hyperthermia were independent factors associated with a pathologically complete response. Initially, a bleomycin regimen was administered, and 5-fluorouracil (5-FU) and the more potent FP regimen (5-FU and cisplatin) were introduced after 1992. Furthermore, preoperative cisplatin use was also an independent factor of overall survival. Combination of chemotherapy using FP plus radiation is superior to radiation alone according to the RTOG 85-01 study (27). Furthermore, the cisplatin dose is related to the response of preoperative CRT for esophageal cancer (29). Cisplatin-based chemoradiotherapy is apparently more potent than other regimens and the current study supports cisplatin as being a key component of preoperative CRT for esophageal cancer. The current study strongly indicates that preoperative cisplatin administration improves patient prognosis as well as the response to CRT. Patients who receive preoperative intraluminal hyperthermia combined with chemoradiotherapy for esophageal cancer show better results than patients who receive preoperative chemoradiotherapy alone (23). The current study revealed hyperthermia to be an independent factor associated with a favorable histological response of the primary tumor. These results suggest that hyperthermia may be a tool for local control of esophageal cancer and preoperative hyperthermia combined with CRT may be useful to increase the resectability of advanced esophageal cancer such as T4 cancer.

The clinical results of esophagectomies for 1,000 patients with esophageal cancer showed preoperative radiotherapy to be an independent risk factor of postoperative pulmonary complications with an odds ratio of 1.61 (6). The current study examining preoperative CRT also revealed preoperative therapy to be associated with postoperative complications including pulmonary complications. The suppression of the immune function is significantly associated with the increase of postoperative complications. Multiple immunological measures were examined in patients with esophageal cancer and the results showed that preoperative treatment induced significant reductions in the total lymphocyte count, phytohemagglutinin response and natural killer activity (30). Furthermore, Heidecke et al. (31) reported that neoadjuvant therapy is associated with significant immunosuppression in the host, specifically with defective proliferation of T-cells after chemoradiotherapy, in comparison to patients undergoing an esophagectomy alone.

Preoperative chemoradiotherapy for esophageal cancer is associated with improvement in patients’ survival. Furthermore, the current study strongly indicates that patients who achieve a pathologically complete response show better prognosis than non-responders. On the other hand, preoperative CRT is closely associated with development of postoperative complications. These observations suggest that indications for preoperative therapy are important and early prediction of responders is essential. 18F-FDP-PET as well endoscopic ultrasound is useful for identification of responders to CRT (32, 33). Another approach to improving outcome after preoperative CRT is the use of molecular assessment of specific characteristics of the tumor. Microarray gene expression profiling of the tumor is a promising method to identify sensitivity to CRT (34). An immunohistochemical evaluation of p53 and p21 expression demonstrated these markers to be useful for the prediction of a pathologically complete response after preoperative CRT.
for SCC of the esophagus (35). Furthermore, the overexpression of epidermal growth factor correlates with a poor response to radiotherapy and EGFR inhibitors are effective as radiosensitizing agents (36). The current study reconfirms that achieving a pathological CR effect is the most significant factor in preoperative CRT. It is important not only to clarify the optimal diagnostic strategy for prediction of the effectiveness of preoperative CRT but also to identify the molecular markers associated with the effect of CRT. The clinical application of molecular targeting therapy, such as EGFR inhibitors to enhance the effect of CRT is also warranted in the future.

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References