Clinical Significance of Chemoradiotherapy and Surgical Resection for cT4 Esophageal Cancer

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Abstract. Aim: To clarify the clinical significance of definitive chemoradiotherapy (CRT) and CRT followed by esophagectomy for cT4 esophageal cancer. Patients and Methods: The treatment results for cT4 esophageal cancer were examined in 81 patients who received definitive CRT [radiation 50-70 Gy, cisplatin and 5-fluorouracil; group I] and 19 patients who underwent esophagectomy after preoperative CRT [40Gy, Group II]. Results: Among the 81 patients in group I, toxicities (grade 3 or 4) were observed in 32 patients, while partial response and complete response were recognized in 8 and 47 patients, respectively. Of the 19 group II patients, an R0 resection was performed in 16 patients, and the mortality rate was 5%. The 5-year survival rates were 19% and 42% in groups I and II, respectively. Conclusion: Long-term survival can be expected after multimodal therapy, even for patients with cT4 esophageal cancer. Esophagectomy is therefore a valid treatment option when down-staging can be achieved.

Esophageal cancer is a biologically and clinically aggressive cancer, and invasion into neighboring organs is frequently present when the disease is first detected. The prognosis of such patients with T4 esophageal cancer is extremely poor (1, 2). On the other hand, this carcinoma is fairly sensitive to radiation, as well as to chemotherapeutic agents such as cisplatin and 5-fluorouracil (5-FU), and multimodal therapy including surgery, chemotherapy and radiotherapy, alone or in combination, has proven to be effective (3). Following the results of the Radiation Therapy Oncology Group trial (RTOG85-01) (4), definitive chemoradiotherapy (CRT) including radiotherapy using a total dose of 50 Gy or more plus cisplatin and 5-FU was established as a treatment strategy for advanced esophageal cancer. Definitive CRT has generally been applied for locally far-advanced esophageal cancer as the standard treatment, however, patients’ prognosis is usually poor (5-9).

Surgical resection after tumor reduction by pre-operative CRT, in which a total dose of 30-40 Gy irradiation and chemotherapy is administered, has also been performed, even for T4 esophageal cancer, and its clinical usefulness has been described in the past (1, 10-16). However, surgical resection for such cases is extremely invasive, with high mortality and morbidity rates (17), and the clinical significance of such treatment is not still fully established. On the other hand, the opportunity to perform salvage surgery for either remnant or recurrent disease after definitive CRT has increased. Nevertheless, salvage surgery for patients with T4 disease is considered to be an extremely high-risk operation, and the prognosis is very poor after an R1/R2 resection [microscopically/macroscopically residual tumor after resection (18)] (19-21).

In the current study, clinical results of 100 patients with T4 squamous cell carcinoma of the esophagus after either definitive CRT or esophagectomy following down-staging by preoperative CRT were evaluated. We also describe the clinical significance of the respective therapies. Furthermore, the clinical results of salvage surgery are also discussed.

Patients and Methods

Patients and treatment strategy. The subjects evaluated in this study were 100 Japanese patients with clinical T4M0 esophageal carcinoma, which was histologically proven to be squamous cell carcinoma by biopsy specimens, and who underwent CRT with or without a subsequent esophagectomy between 2003 and 2009 at the National Kyushu Cancer Center. Our strategy for cT4 esophageal cancer is as follows: Definitive CRT with a total dose...
of 50 Gy or more of irradiation is initially administered to those who would not be able to tolerate surgical resection due to poor general status; for patients in good general condition, preoperative CRT including a total dose of 40 Gy of irradiation is initially performed, and the operability is evaluated at the end of the preoperative CRT; esophagectomy is then performed only when an R0 resection was strongly considered to be possible due to downstaging of the tumor. For other patients, additional CRT is performed as definitive CRT. Among the 100 patients with cT4 tumors, definitive CRT was finally performed for 81 patients (group I), while the other 19 patients (group II) underwent an esophagectomy after preoperative CRT.

Evaluation of tumor staging. The clinicopathological factors were classified according to the classification of the Japan Esophageal Society (18). The depth of invasion was mainly diagnosed using a combination of computed tomography (CT) and double contrast esophagography (22), while endoscopic ultrasonography was subsequently used. The findings of a bronchoscopy and biopsy were also added for the diagnosis of invasion to the tracheobronchial tree. Distant metastases, such as (e.g. to the lung, liver and bone) were detected based on the findings of CT scans of the neck, chest and abdomen, abdominal ultrasonography and bone scintigraphy. Since 2006, 2-fluoro-2-deoxy-D-glucose positron-emission tomography (FDG-PET) has been routinely adopted for initial tumor staging.

Methods used for CRT and surgery. Radiotherapy was initially delivered using equally weighted anterior- and posterior-opposed beams from a 10-MV linear accelerator in 25 fractions of 1.6 Gy (total 40 Gy). As definitive radiotherapy, an additional 20 Gy (total 60 Gy) was administered by two parallel oblique fields or multiple fields to the patients in group I. The irradiation field craniocaudally encompassed the primary tumor with a 3 cm margin. All possible metastatic lymph nodes were included in the radiation field.

In the patients in group II, only preoperative radiotherapy (the first 40 Gy) was performed, followed by surgery 4-6 weeks after the termination of the preoperative CRT. The surgery consisted of a subtotal esophagectomy and regional lymph node dissection, followed by reconstruction using a gastric tube through the retrosternal route with a cervico-right thoracic-abdominal approach (2).

For chemotherapy, cisplatin and 5-FU were intravenously administrated with a daily low-dose regimen (23) before 2008, while a standard-dose regimen (9) was principally used since 2008. The daily low-dose regimen consisted of a 24-hour continuous infusion of 250 mg/m² day of 5-FU combined with a 1-hour infusion of 6 mg/m²/day of cisplatin, while radiation was concurrently administered at 1.6 Gy/day. After a break of two or three weeks, this CRT was repeated for patients who underwent definitive CRT (group I). The standard-dose regimen consists of a slow drip of cisplatin at 70 mg/m² on days 1 and 29, and continuous infusion of 5-FU 700 mg/m²/day on days 1-4 and 29-32 (9). The daily low-dose regimen was administered to 67 patients and the standard-dose regimen was administered to 14 out of the 81 patients who underwent definitive CRT (group I). For all 19 patients who underwent esophagectomy after CRT (group II), the daily low-dose regimen was adopted.

As a follow-up for the definitive CRT, CT, as well as endoscopy with Lugol staining, was performed every four months in the first and second years. Subsequently, these examinations were performed twice a year. The post-operative follow-up was performed mainly by CT scans of the neck, chest and abdomen every four months in the first and second years, then subsequently twice a year until five years after the operation.

Evaluation of toxicities and effects of CRT. Toxicity assessments for all patients were performed based on the National Cancer Institute common toxicity criteria for adverse events (version 4.0) (24). The clinical effect of CRT was based on the response evaluation criteria of The Japan Esophageal Society (18), which was added to the evaluation criteria for primary tumors of the esophagus in the RECIST criteria (25). The histological effect of CRT was also classified based on the criteria of The Japan Esophageal Society (18): Grade 0: Ineffective, no discernible therapeutic effect on the cancer tissue or cells. Grade 1: Slightly effective, apparently viable cancer cells account for one-third 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 one-third of the tumor tissue, while the other cancer cells are severely degenerated or necrotic. Grade 3: Markedly effective, no viable cancer cells are evident, findings are consistent with a pathologically complete response.

Statistical analysis. The differences in the distribution frequencies between the groups were evaluated using Fisher’s exact test or the unpaired Student’s t-test. Survival curves were plotted according to the Kaplan - Meier method, and any differences between two curves were analyzed using the log-rank test. Differences were considered to be significant if the p-value was <0.05. The data were analyzed using the StatView software package (Abacus Concepts, Inc., Berkeley, CA, USA).

Results

Clinical characteristics. Table I summarizes the clinicopathological characteristics of the patients who underwent definitive CRT (group I) and those who underwent esophagectomy after pre-operative CRT (group II). Fifteen patients with cervical esophageal cancer were included in the definitive CRT group; all patients in the pre-operative CRT group had thoracic esophageal cancer. The incidence of node-positive metastasis was higher in the definitive CRT group than in the pre-operative CRT group.

Clinical results of definitive CRT. Among the 81 patients who underwent definitive CRT, 68 patients (84%) completed the initially planned chemotherapy, while 13 patients were unable to complete the full treatment due to acute toxicity. Acute toxicity of grade 3 and 4 was recognized in 28 and four patients, respectively. The toxicities classified as grade 4 were an esophago-pulmonary fistula in 2 patients, and respiratory failure and hyperglycemia in one patient each. The most frequent toxicities of grade 3 were granulocytopenia in 14 patients, followed by general fatigue and allergy in 4 patients each, thrombocytopenia in 3, and pulmonary fistula, anemia, and hemostomatus in one patient each. No treatment-related death was observed.
The radiological imaging of primary as well as metastatic lesions revealed that a complete response (CR) was obtained in 8 patients (10%) and that a partial response (PR) was obtained in 47 patients (58%). Therefore, the response rate was 68%. On the other hand, no change (NC) and progressive disease (PD) were noted in 15 and 11 patients, respectively. Additional chemotherapy was performed after definitive CRT for 40 patients with either a nedaplatin plus 5-FU (27 patients) or cisplatin plus 5-FU (13 patients) regimen.

Figure 1 shows the survival curves after definitive CRT. The median survival was 12 months. The 1-, 2-, 3- and 5-year overall survival rates of the 81 patients were 50%, 30%, 28%, and 19%, respectively. The prognosis was closely related to the clinical efficacy of the definitive CRT. Most of the patients in whom definitive CRT was not effective (NC or PD) died within two years. On the other hand, the 3- and 5-year survival rates were 33% and 22%, respectively, in patients classified into the PR group, and they were 75% and 50%, respectively, in patients who were considered to have a CR (CR versus PR: p=0.049, CR versus NC+PD: p=0.0002, PR versus NC+PD: p=0.0001).

Salvage esophagectomy was performed on 5 patients (2 patients with remnant disease and 3 patients with recurrence) after definitive CRT. An R0 resection was possible in 3 patients. Post-operative pneumonia and a surgical site infection developed in one patient each; however, the postoperative course was fairly good in the other 3 patients. Among the three patients who underwent an R0 resection, two are still alive without recurrence (Table II).

Clinical results of esophagectomy after down-staging by preoperative CRT. Among the 19 patients who underwent esophagectomy after down-staging by preoperative CRT, neutropenia and anorexia classified as grade 3 were recognized in four and one patient, respectively. The clinical efficacy was classified as a PR in 17 patients, while it led to NC in the other 2 patients. An R0 resection was performed in 16 patients; however, the primary tumor could not be completely removed (R2 resection) in the other 3 patients. Post-operative pneumonia developed in three patients, and anastomotic leakage occurred in 2 patients. One patient who developed pneumonia requiring re-intubation died due to a cerebral hemorrhage 26 days after esophagectomy. The surgical mortality and morbidity were 5% and 26%, respectively. Histologically, grade 3 (markedly effective) and grade 2 (moderately effective) activities were recognized in 2 and 7 patients, respectively. Grade 1 (slightly effective) activity was observed in the remaining 10 patients.

Figure 2 shows the overall survival curves after esophagectomy. The median survival was 22 months and the 1-, 3-, and 5-year survival rates were 63%, 42% and 42%, respectively. In the 16 patients who underwent an R0 resection, the 5-year survival rate was 50%, while all three patients who underwent an R2 resection died within one year after esophagectomy (p=0.012). The survival was closely related to the histological efficacy of the CRT. The 3- and 5-year survival rates were both 67% in patients with either grade 2 or grade 3 effects, while they were both 20% in those with grade 1 effects (p=0.017). No statistically significant differences were recognized in the patients’ prognosis regarding clinical node metastasis, although the 5-year survival rates were 55% and 25% in patients with and without node metastasis, respectively (p=0.16).

**Discussion**

**Definitive CRT and salvage esophagectomy.** The prognosis of patients with T4 esophageal cancer is considered to be extremely poor; however, definitive CRT adopting cisplatin-based regimens enables long-term survival in some patients. Recently, more potent CRT regimen using docetaxel associated with cisplatin plus 5-FU was reported (26). The clinical response rate to definitive CRT for T4 esophageal cancer was reported to be 57-81%, and the 1-, 3-, and 5-year survival rates have been reported to be 35-45%, 7-23%, and 7-14%, respectively (1, 5-7, 9, 14). The present study revealed fairly satisfactory results for definitive CRT, with a good response rate (68%), as well as 1-, 3- and 5-year survival rates of 50%, 28%, and 19%, respectively. We have adopted additional chemotherapy using a platinum-based regimen after definitive CRT, and maintained the treatment as long as possible. Furthermore, we performed strict follow-up examinations to detect recurrence as soon as possible for

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Table I. Clinical backgrounds of patients who underwent definitive chemoradiotherapy (CRT) and those who underwent preoperative CRT followed by esophagectomy.

<table>
<thead>
<tr>
<th>Clinical background</th>
<th>Definitive CRT group (n=81)</th>
<th>Preoperative CRT group (n=19)</th>
</tr>
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<tbody>
<tr>
<td>Age, years (Mean±S.D.)</td>
<td>62.7±8.5</td>
<td>62.3±7.6</td>
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<tr>
<td>Gender</td>
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<tr>
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<td>15</td>
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<tr>
<td>Female</td>
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<td>4</td>
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<td>Location of the tumor</td>
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<td></td>
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<tr>
<td>Cervical esophagus</td>
<td>15*</td>
<td>0*</td>
</tr>
<tr>
<td>Upper thoracic esophagus</td>
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<td>0</td>
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<td>8</td>
</tr>
<tr>
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<td></td>
</tr>
<tr>
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<td>22</td>
<td>11</td>
</tr>
<tr>
<td>Positive</td>
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<td>8*</td>
</tr>
<tr>
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</tr>
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<td>9</td>
</tr>
<tr>
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<td>5</td>
</tr>
<tr>
<td>Both</td>
<td>7</td>
<td>5</td>
</tr>
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</table>

*p<0.01 between both groups by Fisher’s exact test.
patients who achieve CR, and aggressive treatments, including salvage surgery. These factors may have resulted in a favorable prognosis after definitive CRT in our patients.

Salvage esophagectomy after definitive CRT is generally considered to be a high-risk operation, associated with critical post-operative complications such as pneumonia and anastomotic leakage. The surgical mortality was reported to be 7-15% (19-21). Especially for T4 tumors, salvage surgery tends to be an R1/R2 resection, and the resulting patient prognosis is extremely poor. On the other hand, long-term survival can be expected if an R0 resection is possible. Seto et al. (1) emphasized that salvage surgery should be considered for residual tumor after definitive CRT, since preoperative judging of the feasibility of R0 resection is difficult, particularly after inflammatory changes due to radiotherapy. We performed salvage operations for five cases with initial T4 tumors, and we adopted a fairly strict indication for such tumors. An R0 resection was not possible in two cases, which indicates the difficulty in making a preoperative assessment of resectability. However, none of our patients experienced critical post-operative complications, and two patients who underwent an R0 resection have survived without recurrence. These results suggest that salvage surgery may be one of the treatment options, even for patients with T4 esophageal cancer, and that long-term survival can be expected if an R0 resection is performed. However, the possibility of an R1/R2 resection cannot be excluded in such cases. Multimodal therapies,
including definitive CRT plus salvage surgery, are therefore considered to be effective for cT4 esophageal cancer.

Esophagectomy after down-staging by pre-operative CRT. Table III summarizes the clinical results of CRT followed by esophagectomy for T4 esophageal cancer (1, 10-16) and when esophagectomy was performed after pre-operative CRT with a radiation dose of 40 Gy or less [except in a study reported by de Manzoni et al. (15)] The patient’s prognosis after an R1/R2 resection was extremely poor, and the surgical mortality and morbidity tended to be high in such cases (17). We have therefore adopted fairly strict indications for esophagectomy for patients initially diagnosed with T4 esophageal cancer: The clinical response to CRT is routinely evaluated at the time of radiation using a dose of 40 Gy, and surgical resection is indicated only when an R0 resection is strongly considered to be possible. Despite such strict indications, the cancerous lesions could not be completely resected (R1/R2) in 3 patients in our study. The incidence of R0 resection rates after pre-operative CRT for T4 cancer was reported to be 39-92% in previous studies (1, 10-16). On the other hand, a pathological CR (grade 3) was recognized in 2 out of 19 patients in our series, while the pCR rates were reported to be 7-29% in previous studies (1, 10-16). It is generally considered to be difficult to achieve a pathological CR after pre-operative CRT for far-advanced esophageal cancer (3). However, satisfactory pathological effects have frequently been observed even in case of cT4 esophageal cancer, when surgical resection was indicated after down-staging.

Regarding prognosis, the 5-year survival rate after esophagectomy of the current study was 42%. Table III shows the inter-institutional differences in the prognosis. The variations may mainly be due to the differences in the surgical indications for the far-advanced cases. However, similar to our current study, 5-year survival rates of more
than 30% were also recorded by other groups (12, 16). Furthermore, as other authors have reported (11, 13, 16), our current study clearly indicates that the prognosis of patients with a pathological CR (grade 3) is especially favorable. These results emphasize that the diagnosis of resectability after CRT for cT4 cancer is difficult, and that the possibility of incomplete resection, which results in a very poor prognosis, remains. However, long-term survival can be expected when an R0 resection can be performed. Therefore, surgery is a valid treatment option when down-staging can be obtained for T4 tumors and an R0 resection is judged to be possible.

**Definitive CRT versus surgery after CRT.** T4 esophageal cancer is considered to be initially inoperable, and two treatment options, definitive CRT and surgery after pre-operative CRT, are currently available. However, it is still controversial as to which treatment is superior in terms of the patients’ survival, as well as quality of life. Especially for responders to pre-operative CRT using a neoadjuvant radiation dose, such as 30-40 Gy, it is difficult to decide whether surgical resection should be indicated at this point or whether subsequent CRT should be performed to provide a definitive dose. Fujita et al. (14) examined the prognosis of patients between these two treatments according to their response to CRT of a neoadjuvant radiation dose. The prognoses of the responders were similar in the two groups, while patients who underwent surgery showed a tendency toward longer survival than the patients who had had no surgery among the non-responders. They therefore recommended that definitive CRT should be used for responders, and that esophagectomy should be performed for non-responders to CRT in the neoadjuvant setting.

On the other hand, Matsubara et al. (27) paid special attention to pathological T4 disease. It was found that not only pre-operative assessment, but also intra-operative macroscopic inspection, was unable to accurately predict pathological T4 disease, which resulted in a poor prognosis. They therefore recommended surgery after pre-operative CRT for all patients, excluding only those with definitive evidence of unresectability. Furthermore, a systemic study examining the surgical outcomes of pathological T4 esophageal cancer clearly indicated historical improvement of the overall survival due to improvement of the curability of the resection (28). In the current study, the prognosis was fairly good, with a 5-year survival of 50% in 8 patients with a CR to definitive chemotherapy, while it was 22% in patients with a PR. On the other hand, the 5-year survival rate was 42% after esophagectomy following pre-operative CRT under the strict surgical indications. It is usually difficult to predict whether a
CR after definitive CRT can be achieved when 30–40 Gy of radiation is administered. We, therefore, recommend surgical resection in case tumor resectability can be strongly expected after pre-operative CRT.

Conclusion

Our present results suggest that long-term survival can be achieved after multimodal therapy in some patients (approximately 20% of patients who received definitive CRT and 40% of patients who underwent esophagectomy after preoperative CRT), even if they have cT4 esophageal cancer. Surgical resection should be considered at the time that 30–40 Gy of radiation is administered, when down-staging can be achieved, and an R0 resection is strongly considered possible.

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References