Comparison of Chemoradiotherapy with Radiotherapy Alone in Patients with Esophageal Adenocarcinoma

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Esophageal cancer/Adenocarcinoma/Chemoradiotherapy/Radiotherapy.

Despite the wide use of definitive chemoradiotherapy (CRT) for locally advanced esophageal adenocarcinoma, there is little evidence that CRT improves the survival of patients with esophageal adenocarcinoma compared with radiotherapy (RT) alone. Therefore, we retrospectively evaluated the outcome of patients with esophageal adenocarcinoma treated by CRT and RT alone. Patients were treated at the Gunma Prefectural Cancer Center (Ota, Japan) and the Gunma University Hospital (Maebashi, Japan). Patients provided written informed consent before treatment. Patients with distant metastases were excluded. CRT consisting of RT, nedaplatin, and 5-fluorouracil has been performed since 2002 when patients have adequate bone marrow, liver, and renal function. Between November 1993 and April 2006, 8 patients were treated by CRT and 12 were RT alone. The median follow-up period of surviving patients was 19 months. CRT group had a significantly higher complete response rate than those RT alone group (87% vs. 33%, $P = 0.05$). Of all patients, 2-year overall survival rate was 41% and the median survival time was 18 months. The 2-year overall survival of patients treated by CRT was 58%, significantly better than 24% of those with RT alone ($P = 0.02$). CRT can improve outcomes of patients with esophageal adenocarcinoma compared with RT alone.

INTRODUCTION

Despite modern multimodality therapy, patients with esophageal cancer have a poor prognosis.1–3 Although surgical resection has been considered a standard of care,1,3 the majority of patients with esophageal cancer are frequently diagnosed at an advanced and inoperable stage.4 Furthermore, since surgery can cause high morbidity, several studies have been reported to investigate less invasive treatment options.5–8 Radiotherapy (RT) alone had been considered an alternative treatment with the potential for organ preservation, although the prognosis was extremely poor with 9.8% of 5-year overall survival.5 Over the last two decades, chemoradiotherapy (CRT) has been recognized as a reliable, non-surgical strategy for locally advanced esophageal carcinoma.6–8

Esophageal cancer has two distinct histological entities: squamous cell carcinoma and adenocarcinoma. In both histological subtypes, definitive or preoperative CRT has been widely performed for locally advanced esophageal cancer.9–11 The advantage of CRT has been shown by the two prospective studies to compare CRT with RT alone.7,10 The Radiation Therapy Oncology Group (RTOG) 85-01 is a landmark phase III study to validate the use of CRT with cisplatin and 5-fluorouracil, compared with RT alone.7 CRT group had a significantly better 5-year overall survival (26%) than RT alone (0%).7 However, most patients had squamous cell carcinoma and adenocarcinoma was observed only in 15 patients, including in 6 treated by RT alone and 9 by CRT. Furthermore, this study did not provide the information whether CRT improves prognosis of adenocarcinoma patients compared with RT alone.7 Another randomized study, EST-1282, demonstrated that CRT involving 5-fluorouracil and mitomycin C improves the overall survival compared with RT alone only in patients with squamous cell carcinoma.10 Although several retrospective studies have been reported to show the efficacy of CRT, they did not compare CRT with RT alone.11–13 To our knowledge, there have been no retrospective or prospective studies to report the efficacy of CRT in esophageal adenocarcinoma compared

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with RT alone.

Therefore, we retrospectively evaluated the outcomes of patients with esophageal adenocarcinoma treated by CRT and RT alone.

**MATERIALS AND METHODS**

**Patient population**

All patients had histologically proven adenocarcinoma of the esophagus and esophagogastric junction (EGJ). Patients were treated at the Gunma Prefectural Cancer Center (Ota, Japan) and the Gunma University Hospital (Maebashi, Japan). Patients provided written informed consent before treatment. Patients with distant metastases were excluded in this study. All cases were assessed according to the American Joint Committee on Cancer staging system. Before treatment, patients were assessed by physical examination, complete blood count, serum chemistries, esophageal endoscopy, computed tomography (CT), barium esophagography, and endoscopic ultrasonography for tumor depth.

**Radiotherapy and chemoradiotherapy**

All patients were irradiated by 10 MV X-rays with a conventional daily fractionation dose of 2 Gy. The initial 40–46 Gy was delivered using anterior-posterior opposed fields. The field of radiation included the 5-cm margin with primary tumor craniocaudally, and 2-cm beyond the radial margins. The boost dose of 10–20 Gy with a shrinking field technique was delivered using oblique parallel opposed fields to avoid the spinal cord. Prophylactic irradiation to the regional lymph nodes was not performed. Before 2002, all patients received RT alone. In contrast, CRT has been performed since 2002 when patients have adequate bone marrow, liver, and renal function. In CRT group, Nedaplatin (45 mg/m²) was administered on day 1 and 8, and 5-fluorouracil (400 mg/m²) was administered by continuous infusion on days 1–5 and 8–12, repeated every 5 weeks.16

**Follow-up**

Patients were assessed at 1 month after completion of the treatment, every 3 months for the first year, and every 6 months thereafter. Complete response (CR) was established by esophageal endoscopy, biopsy specimens, and CT. The date of the first progression and death were recorded.

**Statistical analysis**

Student’s t-test and Mann–Whitney U test were used to evaluate differences in the clinical factors between the CRT and RT alone groups. The primary end point of this study was overall survival which was calculated from the first date of RT to either the date of death or the last follow-up visit. The secondary end points included progression-free survival and local control. Progression-free survival was defined as the period between the first date of RT and the day when disease progression was detected. Overall and progression-free survival curves were calculated using the Kaplan–Meier method and statistically analyzed using the log-rank test. P values < 0.05 were considered statistically significant. All of the analyses were performed with SPSS 11.0 for Windows (SPSS Inc., Chicago, IL).

| Table 1. Patients characteristics | Characteristics | Whole group | RT alone | CRT | RT vs CRT | P value |
|-----------------------------------|----------------|------------|----------|-----|-----------|--------|
| **Age (y)**                       |                |            |          |     |           |        |
| < 70                              |                | 9 (45)     | 4 (33)   | 5 (63) |           | 0.31   |
| ≥ 70                              |                | 11 (55)    | 8 (67)   | 3 (37) |           |        |
| **Gender**                        |                |            |          |     |           |        |
| Male                              |                | 18 (90)    | 10 (83)  | 8 (100) |           |        |
| Female                            |                | 2 (10)     | 2 (17)   | 0 (0) |           | 0.57   |
| **Performance Status**            |                |            |          |     |           |        |
| 0–1                               |                | 15 (75)    | 8 (67)   | 7 (87) |           |        |
| 2                                 |                | 5 (25)     | 4 (33)   | 1 (13) |           | 0.47   |
| **Length**                        |                |            |          |     |           |        |
| < 5.0 cm                          |                | 5 (25)     | 4 (33)   | 1 (13) |           |        |
| ≥ 5.0 cm                          |                | 15 (75)    | 8 (67)   | 7 (87) |           | 0.47   |
| **T stage**                       |                |            |          |     |           |        |
| T1                                |                | 3 (15)     | 2 (17)   | 1 (13) |           |        |
| T2                                |                | 3 (15)     | 3 (25)   | 0 (0) |           |        |
| T3                                |                | 9 (45)     | 3 (25)   | 6 (75) |           |        |
| T4                                |                | 5 (25)     | 4 (33)   | 1 (13) |           | 0.91   |
| **N stage**                       |                |            |          |     |           |        |
| N0                                |                | 9 (45)     | 8 (67)   | 1 (13) |           |        |
| N1                                |                | 11 (55)    | 4 (33)   | 7 (87) |           | 0.05   |
| **Tumor differentiation**         |                |            |          |     |           |        |
| Well/moderately                   |                | 9 (45)     | 7 (58)   | 2 (25) |           | 0.15   |
| Poorly                            |                | 11 (55)    | 5 (42)   | 6 (75) |           |        |
| **Location of primary tumor**     |                |            |          |     |           |        |
| Upper thoracic                    |                | 2 (10)     | 2 (17)   | 0 (0) |           |        |
| Midthoracic                       |                | 2 (10)     | 1 (8)    | 1 (13) |           |        |
| Lower thoracic                    |                | 10 (50)    | 7 (58)   | 3 (38) |           |        |
| EGJ                               |                | 6 (30)     | 2 (17)   | 4 (50) |           | 0.18   |
| **Radiation dose**                |                |            |          |     |           |        |
| Median (Gy)                       |                | 59.0       | 60.0     | 58.0 |           | 0.97   |
| < 60 Gy                           |                | 11 (55)    | 6 (50)   | 5 (62) |           |        |
| ≥ 60 Gy                           |                | 9 (45)     | 6 (50)   | 3 (38) |           |        |

**Abbreviations:** CRT: chemoradiotherapy, RT: radiotherapy, EGJ: esophagogastric junction.
RESULTS

Patient characteristics

Between November 1993 and April 2006, 24 consecutive patients were treated with either CRT or RT alone. Four patients with distant metastases were excluded and 20 patients were analyzed in this study. Twelve patients were treated at the Gunma Prefectural Cancer Center and 8 patients were at the Gunma University Hospital. CRT was performed in 8 patients and RT alone was in 12, respectively. The clinical characteristics of patients for each treatment modality are shown at the Table 1. The median follow-up period for surviving patients was 19 months (range, 2–61). The median age was 70.5 years (range, 46–92 years) and there were 18 male and 2 female patients. Fifteen patients (75%) had a performance status between 0–1, and 5 (25%) had a performance status of 2. A majority of patients (70%) had locally advanced tumor (T3 or T4). Lymph node metastasis was observed in 11 patients (55%). Three patients had stage I, 4 had stage II, 9 had stage III, and 4 had stage IV disease, respectively. The mean tumor length was 6 cm (range, 1–12 cm). Well/moderately and poorly differentiated tumors were observed in 9 (45%) and 11 patients (55%), respectively. The location of primary tumor was mainly at the thoracic esophagus (70%). The median radiation dose was 59 Gy, and 9 patients (45%) received a dose of ≥60 Gy. One patient in RT alone group was treated with high-dose-rate brachytherapy (3 Gy × 3 times) using Ir-192 sources after receiving 60 Gy external beam radiation. No patients under-

| Table 2. Therapeutic effect of RT alone and CRT |
|-----------------------------------------------|
| Therapeutic effect | Whole group | RT alone | CRT | P value |
|---------------------|-------------|----------|-----|---------|
| CR                  | n = 20 (%)  | n = 12 (%) | n = 8 (%) |    |
| 11 (55)             | 4 (33)      | 7 (87)   |    | 0.05    |
| Non-CR              | 9 (45)      | 8 (67)   | 1 (13) |    |

Abbreviations: CRT: chemoradiotherapy, RT: radiotherapy, CR: complete response

![Fig. 1. The overall survival curve of all patients with esophageal adenocarcinoma. The 2-year overall survival was 41% and the median survival period was 18 months.](image)

| Table 3. Clinical characteristics and 2-year overall survival |
|------------------------------------------------------------|
| Characteristics | n  | 2-year OS (%) | P value |
|-----------------|----|----------------|---------|
| All patients    | 20 | 41 (%)         | -       |
| Age             |    |                |         |
| < 70            | 9  | 28             |         |
| ≥ 70            | 11 | 58             | 0.60    |
| Performance status | |          |         |
| 0/1             | 15 | 45             |         |
| 2               | 5  | 30             | 0.35    |
| Length          |    |                |         |
| < 5.0 cm        | 5  | 53             |         |
| ≥ 5.0 cm        | 15 | 39             | 0.84    |
| T stage         |    |                |         |
| T1-T2           | 6  | 44             |         |
| T3-T4           | 14 | 41             | 0.84    |
| N stage         |    |                |         |
| N0              | 9  | 40             |         |
| N1              | 11 | 42             | 0.34    |
| Tumor differentiation | |            |         |
| Well and moderately | 9 | 52             |         |
| Poorly          | 11 | 40             | 0.63    |
| Location of primary tumor | |            |         |
| Thoracic esophagus | 14 | 39             |         |
| EGJ             | 6  | 50             | 0.15    |
| Treatment modality |     |                |         |
| CRT             | 8  | 58             |         |
| RT alone        | 12 | 24             | 0.02    |
| Radiation dose  |    |                |         |
| < 60 Gy         | 11 | 43             |         |
| ≥ 60 Gy         | 9  | 39             | 0.97    |
| Therapeutic effect |     |                |         |
| CR              | 11 | 55             |         |
| Non-CR          | 9  | 26             | 0.01    |

Abbreviations: OS: overall survival, EGJ: esophagogastric junction, CRT: chemoradiotherapy, RT: radiotherapy, CR: complete response
went brachytherapy in CRT group. CRT group had a significantly higher incidence of lymph node metastasis than RT alone group (87% vs. 33%, \( P = 0.05 \)). Significant differences were not detected in other clinical characteristics between the two groups.

**Treatment outcome**

CR rate was 55% for all patients (Table 2). CRT group had a significantly higher CR rate than RT alone group (87% vs. 33%, \( P = 0.05 \)). Other clinical factors, such as performance status, age, tumor length, radiation dose, stages, and tumor differentiation, were not associated with CR rate. Eleven patients died due to tumor progression and 4 patients were alive more than 2 years later. There were no treatment-related deaths and both treatments were well tolerated. The 2-year overall survival for all patients was 41% and the median survival time was 18 months (Fig. 1). The overall survival based on clinical characteristics is shown in Table 3. The 2-year overall survival of patients treated by CRT was 58%, significantly better than 24% of RT alone (Fig. 2, \( P = 0.02 \)). Other clinical factors were not associated with overall survival. Patients with CR had a significantly better survival than those with non-CR (Fig. 3, \( P = 0.01 \)).

Of all patients, 2-year progression-free survival was 16% and the median progression-free survival was 10 months. Although CRT improved the 2-year progression-free survival (25%) compared with RT alone (0%), the difference did not reach statistical significance (\( P = 0.11 \)). Other clinical factors were not associated with progression-free survival.

**DISCUSSION**

CRT is widely performed in esophageal cancer with squamous cell carcinoma and adenocarcinoma. However, there is no clear evidence that CRT improves the outcomes in adenocarcinoma, compared with RT alone.\(^9\) Our study showed that patients with esophageal adenocarcinoma treated by CRT had a significantly better overall survival (\( P = 0.02 \)) and local control (\( P = 0.05 \)) than those receiving RT alone. To our knowledge, this is the first report to show the efficacy of CRT for esophageal adenocarcinoma patients compared with RT alone.

Our study showed that CRT improves outcomes of esophageal cancer. However, some clinicians consider that esophageal adenocarcinoma is less suitable for CRT than squamous cell carcinoma, because adenocarcinoma is generally considered to be radioresistant than squamous cell carcinoma. So far, there are no investigations to compare adenocarcinoma and squamous cell carcinoma treated by definitive CRT regimens, whereas a meta-analysis has shown that evaluated 10 randomized trials comparing preoperative CRT with surgery alone between these two histological subtypes.\(^17\) This study showed that the hazard ratio with preoperative CRT versus surgery alone was 0.75 (0.59–0.95, \( P = 0.02 \)) for esophageal adenocarcinoma and 0.84 (0.71–0.99, \( P = 0.04 \)) for squamous cell carcinoma. They concluded that the estimated survival benefit for preoperative CRT was similar for the both histological subtypes.\(^17\) Given these findings, definitive CRT can be effective for esophageal adenocarcinoma, as well as squamous cell carcinoma.

In our study, CRT significantly increased a CR rate compared with RT alone (87% vs. 33%). This result is consistent with the finding from RTOG 85-11 that persistence of disease was observed in 25% patients treated by CRT and in 40% those treated by RT alone.\(^17\) Furthermore our study showed that CR was related to significantly better overall survival than non-CR (\( P = 0.01 \)). Several trials of preoperative CRT have shown that pathological CR was significantly associated with a better prognosis than non-CR.\(^18–20\) Espe-
cially, Rohatgi et al. reported that pathological CR was associated with better survival and fewer distant metastases than non-CR in adenocarcinoma patients, but not squamous cell carcinoma.\textsuperscript{20} Therefore, local tumor control can be considered as being one of the most important factors for esophageal adenocarcinoma treated by CRT.

In Western countries, the number of esophageal adenocarcinoma patients has rapidly increased in the last few decades.\textsuperscript{21,22} In contrast, the incidence of adenocarcinoma in Japan has remained stable, and the absolute incidence remains much lower than that in Western countries.\textsuperscript{23} Barrett’s esophagus, gastroesophageal reflux disease, and absence of \textit{Helicobacter pylori} (\textit{H. pylori}) infection have been reported as substantial risk factors for esophageal adenocarcinoma.\textsuperscript{24–26} In the Japanese elderly population, the prevalence of \textit{H. pylori} has been reported to be more than 80%.\textsuperscript{27} Therefore, some investigators have hypothesized that the insignificant increase in the incidence of adenocarcinoma in Japan is likely attributed to a higher prevalence of \textit{H. pylori} compared with Western countries.\textsuperscript{23}

Currently, several investigations focus on improving the therapeutic ratio by using novel targeting therapy or chemotherapy.\textsuperscript{28–30} Fortunately, conventional CRT regimens seem to be similarly effective for squamous cell carcinoma and adenocarcinoma. However, due to different biological functions of these histological subtypes, molecular targeted therapy or new combination chemotherapy can result in different responses.\textsuperscript{31,32} In fact, different chemotheraphy according to histologic subtype has been established for advanced non-small cell lung cancer.\textsuperscript{33} In future trials, adenocarcinoma and squamous cell carcinoma should be separately analyzed. RTOG 04-36 is an ongoing randomized trial to evaluate the addition of cetuximab, a monoclonal antibody against epidermal growth factor receptor, to paclitaxel, cisplatin, and radiation in esophageal cancer. In this trial, histology subtypes between adenocarcinoma and squamous cell carcinoma is stratified. This study is expected to validate the efficacy of additional cetuximab for each histological subtype.

There are some limitations of our study, such as its retrospective nature and the small number of patients. Further confirmation with an increasing number of patients is required. However, a randomized study to compare CRT with RT alone cannot be performed, because of ethical considerations.\textsuperscript{9} Therefore, our study can support evidence that CRT is an important strategy for esophageal adenocarcinoma.

In conclusions, our study showed that CRT can improve outcomes compared with RT alone in patients with esophageal adenocarcinoma. However, additional investigations are warranted to establish the optimized treatments for esophageal adenocarcinoma.

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