A single institutional phase III trial of preoperative chemotherapy with hyperfractionation radiotherapy plus surgery versus surgery alone for resectable esophageal squamous cell carcinoma

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Background: We conducted a prospective randomized controlled trial comparing surgery alone (S) with concurrent chemoradiotherapy followed by surgery (CRT-S) for resectable esophageal squamous cell carcinoma (SCC) based on our previous report.

Patients and methods: One hundred and one patients with stage II/III esophageal SCC were randomized to receive either S (50 patients) or CRT-S (51 patients). The chemoradiotherapy (CRT) consisted of cisplatin 60 mg/m² intravenously (i.v.) on day 1, 5-fluorouracil (5-FU) 1000 mg/m² i.v. on days 2–5, cisplatin 60 mg/m² i.v. on day 22 combined with radiation therapy (45.6 Gy, 1.2 Gy b.i.d. on days 1–28). Surgery was performed 3–4 weeks after radiotherapy was completed. For patients with disease that was stable or responsive to CRT, three additional cycles of chemotherapy (cisplatin 60 mg/m² i.v. on day 1, 5-FU 1000 mg/m² on days 2–5 every 4 weeks) were given after surgical resection.

Results: The median age was 62 years. The toxicity of CRT was acceptable and did not affect the post-operative morbidity and the duration of hospital stay. Clinical response was 86% including 21% of complete response (CR) rate. Pathological CR was achieved in 43% [95% confidence interval (CI) 27–59] of the patients who underwent surgery after CRT. At a median follow-up of 25 months, overall survival (OS) was 27.3 months in S and 28.2 months in CRT-S (P = 0.69). Event-free survival (EFS) at 2 years was 51% in S and 49% in CRT-S (P = 0.93). This trial, which was statistically powered to detect a relatively large difference in 2-year survival rate from 30% to 50% with 80% power, was discontinued at interim analysis because of the unexpectedly high drop-out rate for esophagectomy (31%) and resultant excessive locoregional failure rate in CRT-S arm (22% versus 12%, P = 0.31), though it was not statistically significant.

Conclusion: Although preoperative CRT induced high clinical and pathological response, there was no statistically significant benefit in OS and EFS.

Key words: combined modality therapy, esophageal cancer, neoadjuvant therapy, randomized controlled trial, squamous cell carcinoma

Introduction

Treatment for patients with esophageal cancer remains unsatisfactory [1]. Although surgery alone or chemoradiotherapy (CRT) have been generally accepted as reasonable options for patients with locoregional esophageal cancer, 5-year survival rate with either management is ~20% [2, 3]. Given the limited success of single modality treatment using radiotherapy or surgery for the primary management of esophageal cancer, efforts have led to the investigation of multimodality therapies, including combinations of chemotherapy, radiotherapy and surgery.

Several non-randomized trials report survival rates that are more than two-fold higher than those reported in past studies for esophageal resection alone [4–8]. However, a limited number of phase III trials on neoadjuvant CRT followed by surgery versus surgery alone have produced conflicting results, contributing little to justify the routine use of preoperative CRT [9–15].

Between 1993 and 1996, we conducted a prospective phase II study of preoperative CRT consisting of 5-fluorouracil (5-FU)/ cisplatin and 46.5–48 Gy of hyperfractionation radiotherapy followed by surgery for patients with resectable esophageal squamous cell carcinoma (SCC) (52 patients) [16]. The results were promising; the median survival was 22 months with a pathological complete response rate of 43%. When compared with a matched historical control (40 patients), there was significant survival benefit in the multimodality arm (P = 0.04). Based on this
phase II trial, we conducted a prospective phase III study of concurrent CRT followed by surgery (CRT-S) versus surgery alone (S) for patients with resectable esophageal SCC. The primary end point was overall survival (OS). Secondary end points were event-free survival (EFS), pathological response to CRT and pattern of failure.

Patients and methods

Patients

Patients with previously untreated, biopsy-proven invasive SCC of the esophagus were eligible. Before registration, a multidisciplinary team evaluated each patient to determine potential resectability and operability. Eligibility criteria included the following: clinically resectable esophageal carcinoma (stage IIA, IIB and III; T2–3N0M0 and T1–3N1M0 according to the American Joint Committee on Cancer classification) [17]; ≥18 years of age; Eastern Cooperative Oncology Group (ECOG) performance status of ≥2; adequate bone marrow reserve consisting of a white blood cell (WBC) count of >3500 cells/µl and a platelet count of >100,000/µl; adequate renal function with serum creatinine level of <1.5 mg/dl or creatinine clearance of >50 ml/min; normal liver function with serum bilirubin level of <1.5 mg/dl; and having no history of prior malignancy, excluding surgically cured basal cell carcinoma of the skin. Patients were not eligible if the primary tumor was located in the cervical esophagus (upper border, <18 cm from the incisor teeth) or if there were cervical or celiac lymph node involvement or evidence of distant metastasis or if they had previously undergone treatment for esophageal carcinoma. Eligible patients were registered to the Asian Medical Center Esophageal Cancer Study Group Data Registry and randomly allocated to either CRT-S or S after stratification for age (<60 years or ≥60 years) and performance status (PS ≤1 or PS ≥2) using permuted-block design. The institutional review board at the Asian Medical Center approved the protocol, and patient’s written informed consent was obtained.

Pretreatment evaluation

Pretreatment evaluation included a medical history review and detailed physical examination, assessment of ECOG performance status, complete blood cell count with differential, liver function test, creatinine levels and clearance, electrocardiogram. ²⁰¹Th myocardial perfusion scan or echocardiography, pulmonary function test, chest radiography, barium esophagography, gastrofiberscopy with biopsy, endoscopic ultrasonography (EUS), computed tomography (CT) of the chest and upper abdomen, bone scan, and fiberoptic bronchoscopy in cases of upper and middle thoracic esophageal cancer.

Neoadjuvant chemoradiotherapy followed by esophagectomy (CRT-S)

Neoadjuvant chemotherapy consisted of cisplatin 60 mg/m² by intravenous (i.v.) infusion over 5 h on days 1 and 21 and 5-FU 1000 mg/m² daily as a continuous i.v. infusion for 4 days from days 2–5. Radiotherapy was delivered twice a day up to a dose of 45.6 Gy in 38 fractions of 1.2 Gy with a minimum of 6 h between treatments. Patients underwent simulation by standard methods utilizing esophagography, esophagography and CT. The superior and inferior borders of the field were 7 cm beyond the primary carcinoma whereas the lateral borders of the field were 2 cm beyond the borders of the primary tumor. Supraclavicular lymph nodes were routinely encompassed in upper thoracic esophageal cancers and celiac nodes in distal or middle thoracic esophageal cancers. Radiotherapy was administered with a 15-MV linear accelerator. Toxic effects were assessed and graded according to the World Health Organization (WHO) toxicity criteria at least once a week. Chemotherapy and radiotherapy were withheld if the granulocyte count was <1000 cells/µl or if the platelet count was <50,000 cells/µl, and were not resumed until both the granulocyte and platelet count recovered to >1500 cells/µl and 75,000 cells/µl, respectively. For grade 2 or worse renal toxicity, cisplatin was withheld until the creatinine value recovered to <1.5 mg/dl, at which point cisplatin was resumed at 50% of the initial dose.

For patients with cancer-induced dysphagia to soft diet, we preferentially performed the placement of an esophageal stent when the patient began chemotherapy. For patients whose oral intake was <1000 Cal/m²/day during treatment, enteral and parenteral nutrition was administered.

Surgical resection was carried out 3–4 weeks after the end of radiotherapy. To proceed with surgery, patients were required to have adequate bone marrow recovery (defined as WBC count ≥3500/µl and platelet count ≥100,000/µl) and no evidence of unresectable disease after repeated chest and abdominal CT scanning.

For patients with disease that was stable or responsive to CRT, three additional cycles of postoperative chemoradiotherapy (cisplatin 60 mg/m² i.v. on day 1, 5-FU 1000 mg/m² i.v. on days 2–5) were given within 4–6 weeks after surgical resection.

Immediate esophagectomy (S)

Abdominal–right thoracic approach (Ivor–Lewis) or right thoracic–abdominal–cervical approach (McKeown) was performed. The proximal and distal margins had to be at least 6–8 cm from the gross tumor. Pathological examination of a frozen section of the resection margin before completion of the surgery was performed. En bloc lymph node dissection included the periesophageal, infracarinal, posterior mediastinal and paracardiac lymph nodes, and those located along the lesser gastric curvature and at the origin of the left gastric artery, celiac trunk, common hepatic artery and splenic artery. Restoration of continuity by esophagogastric anastomosis or colonic interposition with a cervical anastomosis was used. Resections were classified as complete when all gross tumor tissue was removed and microscopical examination revealed all margins to be free of tumor (R0). Resections were considered incomplete either when microscopical examination revealed positive margins (R1) or when there was residual gross disease (R2). Patients who had an incomplete surgical resection were treated with additive postoperative radiotherapy with or without chemotherapy.

Evaluation of response after CRT

After the preoperative treatment, patients were re-evaluated with endoscopy, EUS and CT scanning. The response was considered complete (CR) when no radiographical or sonographical evidence of disease was seen, no residual tumor was found during esophagosity and the biopsy was negative. Otherwise, the response was classified as partial (PR, >50% reduction of tumor size on CT scan), stable disease (SD), or disease progression (PD). After surgical resection, a pathological complete response (pCR) was defined as the absence of residual tumor in the esophagus and lymph nodes.

Follow-up evaluation and assessment of end points

Follow-up after treatment included medical oncology visit at 3-month intervals for the first 2 years and every 6 months from 3–5 years. During the follow-up visit, patients underwent CT scan and endoscopy every 12 months and whenever clinically indicated.

Statistical analysis

The two treatment groups were compared with respect to base-line characteristics with use of the t-test or the chi-squared test. When necessary, Fisher’s exact test was also used. Survival time was calculated from the date of randomization to the date of death due to any cause. EFS was defined as the time from the date of randomization to the date of first observation of disease progression, or relapse, or death due to any cause. The survival analysis was performed by the actuarial Kaplan–Meier method [18], and differences between the
curves were analyzed using the log-rank test [19]. Sample-size calculations (Freedman’s method [20]) showed that we needed 190 patients to detect an improvement in median survival from 15 to 22 months, corresponding to an increase in the 2-year survival rate from 30% to 50% (hazard ratio 0.625), among patients undergoing CRT-S with 80% power and two-sided α of 0.05. We scheduled a formal interim analysis to be performed when 100 patients were accrued. If survival difference is significant (P <0.0054) for interim analysis [21], the study is scheduled to stop.

Results

Patient characteristics

Between March 1999 and May 2002, a total of 123 patients with locoregional esophageal SCC were observed at our medical oncology unit. Twenty-two patients were ineligible: five patients had a clinical T4 tumor (definite bronchial invasion in four, and invasion to aorta in one); four patients refused to enrol on to the protocol; three patients had early esophageal cancer (T1N0M0); two patients had already undergone radiotherapy for esophageal cancer; two patients had concomitant malignancies (advanced gastric cancer); two patients had other medical illness with poor general condition contraindicating chemotherapy and surgery (pulmonary tuberculosis and compromised lung function); and one patient had cervical esophageal cancer. One hundred and one patients fitting all the eligibility criteria were enrolled; 50 assigned to S group and 51 assigned to CRT-S group. Pretreatment characteristics were well balanced between the two treatment groups, except for a slightly higher proportion of patients without clinical lymph node involvement in the S group (P = 0.13; Table 1).

Compliance and clinical response to CRT

Of the 51 patients assigned to CRT-S, 49 patients completed the scheduled CRT. It was interrupted in two patients due to unexplained sudden cardiac death and neutropenia/sepsis, respectively. CRT was delayed in 14 patients; reasons were neutropenia (six patients), mucositis (three), thrombocytopenia (one), intercurrent disease (two, acute myocardial infarction in one and unstable angina in the other), and personal cause (two). The accrual and treatment summary is depicted in Figure 1. The most frequent hematological toxicity was neutropenia and the most common non-hematological toxicities were nausea/vomiting and esophagitis. We could assess the clinical response to neoadjuvant CRT in 47 patients in CRT-S group. The numbers of patients by type of clinical response were as follows: CR, 11 (22%); PR, 33 (65%); SD, two (4%); and PD, one (2%).

Surgical results and pathological responses

Data on surgical results are listed in Table 2. Among S group, 48 patients (96%) underwent surgery, while 35 of the 51 patients (69%) randomized to CRT-S underwent surgery (P <0.01). The most frequent reason for no surgery was patients’ refusal in both groups. Four patients in CRT-S group were not operated on for the following reasons: esophagobronchial fistula in one patient; metastatic lung nodules in one; and inoperable concurrent morbidity in two patients.

In CRT-S group, all the patients who underwent esophagectomy achieved R0 resection. Pathological complete response was achieved in 43% [15 of 35, 95% confidence interval (CI) 27–59] of the patients who underwent surgery after CRT. In

### Table 1. Pretreatment characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CRT-S</th>
<th>S</th>
<th>Total</th>
</tr>
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<tbody>
<tr>
<td>Total no. of patients</td>
<td>51</td>
<td>50</td>
<td>101</td>
</tr>
<tr>
<td>Median age, years (range)</td>
<td>63 (42–73)</td>
<td>63 (39–75)</td>
<td>63 (39–75)</td>
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<tr>
<td>Sex (male/female)</td>
<td>46/5</td>
<td>47/3</td>
<td>93/8</td>
</tr>
<tr>
<td>ECOG PS 0/1</td>
<td>1/50</td>
<td>4/46</td>
<td>5/96</td>
</tr>
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<td>2</td>
<td></td>
</tr>
<tr>
<td>Middle third</td>
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<td>30</td>
<td>58</td>
</tr>
<tr>
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<td>17</td>
<td>33</td>
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<td>3</td>
<td>8</td>
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<tr>
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<td>2</td>
<td>10</td>
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<tr>
<td>MD</td>
<td>31</td>
<td>31</td>
<td>62</td>
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<tr>
<td>PD or UD</td>
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<td>7</td>
<td>16</td>
</tr>
<tr>
<td>NA</td>
<td>9</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Primary tumor length</td>
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<tr>
<td>&lt;6 cm</td>
<td>26</td>
<td>31</td>
<td>57</td>
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<tr>
<td>≥6 cm</td>
<td>25</td>
<td>19</td>
<td>44</td>
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<tr>
<td>Duration of dysphagia, months (range)</td>
<td>2.5 (0–12)</td>
<td>1.7 (0–7)</td>
<td>1.8 (0–12)</td>
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<td>Severity of dysphagia</td>
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<td>5</td>
</tr>
<tr>
<td>Dysphagia to solid food</td>
<td>30</td>
<td>28</td>
<td>58</td>
</tr>
<tr>
<td>Dysphagia to liquid food</td>
<td>16</td>
<td>13</td>
<td>29</td>
</tr>
<tr>
<td>Dysphagia even to saliva</td>
<td>4</td>
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<tr>
<td>Weight loss</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>None/NA</td>
<td>22/2</td>
<td>20/5</td>
<td>42/7</td>
</tr>
<tr>
<td>&lt;10%</td>
<td>16</td>
<td>19</td>
<td>35</td>
</tr>
<tr>
<td>≥10%</td>
<td>11</td>
<td>6</td>
<td>17</td>
</tr>
<tr>
<td>Serum albumin, g/dl</td>
<td>3.9 ± 0.4</td>
<td>3.8 ± 0.5</td>
<td>3.9 ± 0.4</td>
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<td>Clinical stage</td>
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</tr>
<tr>
<td>II A</td>
<td>14</td>
<td>22</td>
<td>36</td>
</tr>
<tr>
<td>II B</td>
<td>12</td>
<td>10</td>
<td>22</td>
</tr>
<tr>
<td>III</td>
<td>25</td>
<td>18</td>
<td>43</td>
</tr>
<tr>
<td>N0</td>
<td>14</td>
<td>22</td>
<td>36</td>
</tr>
<tr>
<td>N1</td>
<td>37</td>
<td>28</td>
<td>65</td>
</tr>
</tbody>
</table>

CRT-S, chemoradiotherapy followed by surgery arm; ECOG PS, Eastern Cooperative Oncology Group performance status; MD, moderately differentiated; NA, not available; PD or UD; poorly differentiated or undifferentiated; S, surgery alone arm; WD, well differentiated; WHO World Health Organization.
S group, 42 of 48 surgical attempts were R0 resections with four R1 and two thoracotomy alone. Esophagectomy was curative in more patients in the CRT-S group ($P = 0.037$). Peri-operative deaths (within 30 days of surgery) occurred in one patient in each group. There were no significant differences in the postoperative morbidity ($P = 0.82$) and the duration of in-hospital stay between the groups ($P = 0.72$). Pathologically determined disease stage after curative resection according to treatment group is shown in Table 3. Comparison of the two groups revealed a significantly lower stage of disease after CRT-S in T stage ($P < 0.001$), N stage ($P < 0.001$), and combined TNM stage ($P < 0.001$) determined pathologically.

Among patients who underwent esophagectomy after CRT, 21 (60%) patients received postoperative chemotherapy. The most frequent reason for non-compliance to postoperative chemotherapy was patients’ refusal (nine patients). The other reasons included postoperative complications (three patients; pneumonia, empyema and hepatitis), concomitant unstable angina pectoris (one patient) and postoperative death (one patient). A median of three cycles of chemotherapy (range 1–3) were administered. Adverse reaction to chemotherapy, which included neutropenia, thrombocytopenia, mucositis and nausea/vomiting, was tolerable and there was no postoperative chemotherapy-related death.

**Overall survival and event-free survival**

Forty-one patients died during the study. With a median follow-up of 25 months (range 4–46 months) for all patients, median OS was 27.3 months (95% CI 15.9–38.7) in S and 28.2 months in CRT-S group ($P = 0.69$; hazard ratio 0.88; 95% CI 0.48–1.63; Figure 2). Survival rate at 2 years was 57% in S compared with 55% in CRT-S group. There was no difference in EFS between groups; EFS at 2 years was 51% in S and 49% in CRT-S group ($P = 0.93$; hazard ratio 0.98; 95% CI 0.55–1.72; Figure 3). We saw no evidence that effect of CRT was significantly beneficial in accordance with age, clinical stage, lymph node involvement and weight loss. To help determine if the increase in the number of patients who refused surgery was the factor responsible for the lack of survival benefit, a separate survival analysis was performed that included only patients who received the assigned treatment. Although there was not a statistically significant difference, there was a trend in favor of CRT-S in OS and EFS ($P = 0.15$ and 0.11, respectively).

Of the clinical parameters, T stage [$P = 0.032$; relative risk (RR) 0.500; 95% CI 0.266–0.938], N stage ($P = 0.024$; RR 0.400; 95% CI 0.170–0.936) and weight loss (>10% over 3 months; $P = 0.002$; RR 0.309; 95% CI 0.154–0.618) were significant prognostic factors for OS. The extent of surgery (Ivor–Lewis operation versus McKeown operation) did not have an impact on OS ($P = 0.99$). Multivariate analysis showed that only weight loss was an independent prognostic factor for OS ($P = 0.02$; RR 0.330; 95% CI 0.120–0.855).

**Pattern of failure, cause of death and early interruption of trial at interim analysis**

The survival status, the crude patterns of first failure and causes of death are listed in Table 4. Among 37 patients whose tumors developed relapse or progression, 13 (35%) had exclusively locoregional failure, 18 (49%) had distant metastasis and six (16%) had both. For the patients in CRT-S group, 37% (19 of 51) of patients had relapse or progression, which is comparable with that of S group (36%, 18 of 50). Considering any locoregional relapse, 11 (22%) patients in CRT-S group had relapses, and six (12%) patients in S group had relapses ($P = 0.31$). No difference was found in the distant metastasis rate between the groups (22% in
After interim analysis, we were concerned that our CRT regimen would have an adverse impact on survival through the increased drop-out rate of esophagectomy and resultant unexpectedly high rate of locoregional failure and so the study was discontinued.

**Discussion**

The rationale to use CRT before surgery includes the elimination of micrometastases, drug delivery through intact tumor blood vessels and improvement of primary tumor resectability [1]. Combined modality regimens, utilizing 5-FU-based chemotherapy and concurrent radiotherapy, have undergone extensive phase II and several phase III trials in resectable esophageal cancer. Nonrandomized studies suggest that this approach may improve locoregional control, and select studies have demonstrated prolonged survival in patients undergoing CRT and esophagectomy compared with historical reports of patients treated with esophagectomy alone [4–8]. Unfortunately, such improved outcomes have not been confirmed in phase III studies. Several well-known randomized studies on the benefit of neoadjuvant CRT produced conflicting results. So far, six of seven randomized trials failed to show that neoadjuvant CRT was associated with a survival advantage [9–15]. Only one study, in
which survival in the surgery-alone group was very poor, showed an OS benefit associated with neoadjuvant CRT [12]. Because of the weaknesses of these studies (underpowered inadequate study design, doubtful staging accuracy and stratification, possible unbalanced randomization, variable radiation doses and its delivery, variable chemotherapy regimens and relatively poor outcome of surgery-alone group), the true efficacy of induction CRT for esophageal cancer remains unclear and controversial. However, survival following neoadjuvant CRT is higher than that following surgery alone in every trial. A recently reported meta-analysis, although not performed from individual data, revealed that neoadjuvant CRT improved 3-year survival (odds ratio 0.66, \( P = 0.038 \)) and reduced locoregional tumor recurrence (odds ratio 0.38, \( P = 0.0002 \)) compared with surgery alone [22]. These findings suggest that neoadjuvant therapy may be beneficial and therefore motivate further investigation.

Our trial demonstrated that for patients with resectable esophageal SCC, concurrent chemotherapy with hyperfractionation radiotherapy before surgical resection does not offer a local/regional control or survival advantage. However, we do not think that our study failed to demonstrate superiority for CRT-S. The reason for the lack of benefit in the CRT-S arm can be explained in several ways. At first, the control arm did better than expected; the median survival time for the surgery-alone group was 27.3 months with a 2-year survival rate of 57%. In a larger trial in the USA, Intergroup 113, and the largest trial in the UK, preoperative chemotherapy was compared with surgery alone [23, 24]. The median survival times for the surgery-only control arms were 16.1 months with 3-year survival rate of 26% and 13.3 months with 2-year survival rate of 34%, respectively. In the largest trial comparing preoperative CRT conducted in Australia, the median survival for the surgery-alone control arm was 18.5 months with 3-year survival rate of 30% [15]. In our phase II trial, the median survival for surgery-only historical control was 15 months and 2-year survival rate was 28% [16]. In this trial, we used trans-thoracic esophagectomy with extended en bloc lymphadenectomy. Even though the evidence is not yet decisive, extended resection is believed to reduce the rate of locoregional recurrence, thereby prolonging disease-free and overall survival [25]. The possible benefit of neoadjuvant CRT would necessarily depend to a certain degree on the quality of lymphadenectomy. Extended resection could diminish the potential benefit of preoperative chemoradiotherapy. Secondly, when comparing the CRT-S versus S arm, there was a significant difference in the number of patients who actually underwent esophagectomy, which has been considered as a standard curative treatment modality for these patients. Among S arm, 96% underwent surgery, while 69% of the patients randomized to CRT-S arm underwent esophagectomy (\( P < 0.01 \)).

In the US trial, 40% of patients registered in the preoperative chemotherapy group could not undergo surgery or had no tumor resection, compared with 15% of patients in the surgery-alone group [23]. In the MRC trial, which demonstrated survival benefit of neoadjuvant chemotherapy, the corresponding numbers were 13% and 17%, respectively [24]. This finding may explain why the US trial failed to demonstrate the benefit of preoperative chemotherapy. Patient refusal after achieving symptom relief, deterioration of overall condition and tumor progression precluded surgery in one-third of patients in the CRT-S arm. This factor may have contributed to the lack of significant benefit for patients who were assigned to receive CRT before surgery in this trial.

In order to overcome tumor cell repopulation and reduce preoperative treatment time, we used hyperfractionation radiotherapy [26, 27], which could also spare normal tissue from late radiation damage [28]. Our regimen led to a pCR rate of 43%, which is the same as that of our previous phase II trial (43%) and high compared with the results previously obtained with a combination using 5-FU and cisplatin (7–33%) [4, 9, 14, 29, 30]. In non-randomized trials of CRT using hyperfractionation radiotherapy, encouraging results have been reported [31, 32]. Even though it

### Table 4. Survival status, sites of first failure and cause of death

<table>
<thead>
<tr>
<th>Category</th>
<th>CRT-S</th>
<th>S</th>
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<tbody>
<tr>
<td>Alive</td>
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<td></td>
</tr>
<tr>
<td>Without evidence of relapse or disease</td>
<td>25</td>
<td>28</td>
</tr>
<tr>
<td>progression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With evidence of disease relapse</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Nature of first failure</td>
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<td></td>
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<tr>
<td>Locoregional failure</td>
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<td>5</td>
</tr>
<tr>
<td>Distant metastasis</td>
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<td>12</td>
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<tr>
<td>Local failure and distant metastasis</td>
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<tr>
<td>Deaths</td>
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<td>Cancer-related</td>
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<tr>
<td>Death from other cause</td>
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<td>2</td>
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<tr>
<td>Death from unknown cause</td>
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</tbody>
</table>

CRT-S, chemoradiotherapy followed by surgery arm; S, surgery alone arm.

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Figure 3. Event-free survival.

Table 4. Survival status, sites of first failure and cause of death

<table>
<thead>
<tr>
<th>Category</th>
<th>CRT-S</th>
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<td>Alive</td>
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<tr>
<td>Without evidence of relapse or disease</td>
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<td>progression</td>
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<td>With evidence of disease relapse</td>
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<tr>
<td>Distant metastasis</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Local failure and distant metastasis</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Deaths</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer-related</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>CRT-related</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Surgery-related</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Secondary primary cancer</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Death from other cause</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Death from unknown cause</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

CRT-S, chemoradiotherapy followed by surgery arm; S, surgery alone arm.
has not been shown to be superior to conventional radiotherapy in randomized trials, hyperfractionation radiotherapy and con-
current chemotherapy may be responsible for a high rate of pCR, which is prerequisite for long-term survival [4, 5, 14]. Among
the 51 patients in the CRT-S arm, two cases of early death, one of
neutropenic sepsis and the other of sudden cardiac death, occurred
and CRT was delayed in 24% of the patients due to CRT-related
toxicity or intercurrent disease. This may mean ~30% of the
patients who are not compliant to planned treatment due to acute
toxicities may have precluded the acceptance of surgery. How-
ever, we do not consider that our CRT regimen is too toxic to
exclude esophagectomy. The most frequent reason (63%) for no
surgery was patients’ refusal to take the surgery-associated risk
after symptom improvement. The total prescribed dose was cis-
platin 120 mg/m² and 5-FU 4000 mg/m² over 3 weeks and total
radiation dose of 45.6 Gy in 1.2 Gy twice-daily fractions, which
was modified from our original CRT regimen to improve patients’
compliance and tolerance [16] and was similar or lower in dose
of 5-FU/cisplatin compared to previous trials using the same
chemotherapeutic agents [4, 7, 8, 10, 14, 29]. Although the major-
ity of patients developed radiation esophagitis, it was generally
well tolerated and manageable. The contribution of the hyper-
fractionation radiotherapy schedule to the toxicity of the current
trial is unclear. Other CRT studies have reported similar toxicities
whether altered fractionation radiotherapy was used or not [4, 33].

Although survival analysis per actual treatment might be biased,
there was a stronger trend for better OS and EFS in the CRT-S arm
compared with the S arm. With a median follow-up of 25 months,
the median OS and EFS were not reached in the CRT-S arm, and
in the S arm were 31.8 and 25.4 months, respectively (P = 0.15
and 0.11). In line with other studies [10–14, 22], our study showed
that patients treated with CRT-S were more likely to have a com-
plete resection performed (P = 0.036). This suggests that neoad-
juvant CRT downstages tumors and facilitates complete
resection. We also confirmed that preoperative CRT did not affect
the postoperative morbidity, the duration of postoperative hospital
stay or mortality (P = 0.53, 0.72 and 0.99, respectively).

After the scheduled interim analysis, there was concern about
the study design and poor patients’ compliance to surgery. The
prior phase II trial conducted at our institution showed that the
median survival was 24 months in the multimodal arm in compar-
ison with 15 months for surgery-alone historical control (odds
ratio 0.625, P = 0.044) [16]. Although there have been conflicting
results, SCC is more likely to be sensitive to CRT compared with
adenocarcinoma and our patients group consisted of SCC exclu-
sively [1, 15]. These findings made us assume a large difference in
OS, which could not be realized in this trial. The numbers of
patients recruited are insufficient to prove the difference to be
significant. The treatment scheme of preoperative CRT followed
by surgery would have an adverse impact on survival through the
increased drop-out rate of esophagectomy after CRT and
resultant unexpectedly high rate of locoregional failure compared
to S alone (22% versus 12%, P = 0.31), although it was not statis-
tically significant. Among any locoregional failure in the CRT-S
arm (13 patients), only three failures (9%) occurred in patients
who underwent esophagectomy after CRT. As mentioned above,
the main reason why no surgery was undertaken was patient
refusal after symptom improvement. This fact led us to develop a
preoperative education program to reduce patients’ anxiety to
esophagectomy and to improve individual patient knowledge on
esophageal cancer treatment. In addition, our hospital environ-
ment was changed during the study period. Today, it is not easy
for us to permit scheduled admission for patients assigned to the
CRT-S arm that included in-hospital 5-FU continuous infusion.
This has deteriorated patients’ compliance to treatment further.
Therefore we decided to stop this study and are now planning neo-
adjuvant CRT including capecitabine in lieu of 5-FU infusion.

In conclusion, although preoperative CRT including cisplatin
and 5-FU induced high clinical and pathological response, there
was no significant benefit in OS and EFS. The fact that about one-
third of the CRT-S arm did not undergo surgical resection may
suggest that the benefit of neoadjuvant CRT can be compromised
during surgery, which plays the main role in preoperative CRT-S,
is omitted. Considering a tendency for better outcome in pre-
operative CRT based on survival per actual treatment arm, further
efforts for optimal combination of CRT before surgery and pre-
operative education program to reduce surgery-associated anxiety
are needed to increase patient compliance to surgical resection.

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