Long-term Follow-up of a Randomized Phase II Study of Cisplatin/5-FU Concurrent Chemoradiotherapy for Esophageal Cancer (KROSG0101/JROSG021)

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Objective: Long-term survival and late toxicities of a randomized Phase II study of chemoradiotherapy for esophageal cancer were analyzed.

Methods: Eligible patients were <75 years old and performance status 0–2, and had Stages II–IVA esophageal cancer. For arm A (short-term infusion), cisplatin 70 mg/m² Days 1 and 29 and 5-fluorouracil 700 mg/m² Days 1–5 and 29–33 were given concurrently with radiotherapy of 60 Gy/30 fr/7 weeks (1 week split). For arm B (protracted infusion), cisplatin 7 mg/m² Days 1–5, 8–12, 29–33 and 36–40, and 5-fluorouracil 250 mg/m² Days 1–14 and 29–42 were given with the same radiotherapy. Two cycles of consolidation cisplatin/5-fluorouracil chemotherapy were given to both arms.

Results: Between 2001 and 2006, 91 patients were enrolled; 46 were randomized to arm A, and 45 to arm B. The 2- and 5-year overall survival rates for arm A were 46 and 35% (95% confidence interval: 22–48%), while those for arm B were 44 and 22% (11–35%), respectively. Excluding four patients with early death, seven (17%) patients in arm A and eight (18%) in arm B showed late toxicities of Grade 3 or more. Most of the toxicities were cardiac or pleural toxicities. Patients with severe late toxicities often had coexistent hypothyroidism. There were three patients with a secondary malignancy possibly related to treatment.

Conclusions: Low-dose protracted infusion chemotherapy with radiotherapy is not superior to full-dose short-term infusion chemotherapy with radiotherapy for esophageal cancer. Late toxicities, including cardiac and pleural toxicities, hypothyroidism and secondary malignancy, should be carefully monitored.

Key words: esophageal cancer – chemoradiotherapy – late toxicities – hypothyroidism – secondary malignancy

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INTRODUCTION

For esophageal cancer, a significant improvement in local control and overall survival was achieved with concurrent chemoradiotherapy (CRT) as compared with radiotherapy (RT) alone (1–3). To improve these results, a Phase III trial comparing standard dose RT (50.4 Gy) and high-dose RT (64.8 Gy) concurrently combined with 5-fluorouracil (5-FU)/cisplatin was conducted (4). In the INT0123 trial, the high-dose arm did not offer a survival benefit compared with the standard dose arm (4). Thus, at present, four cycles of full dose 5-FU/cisplatin combined with 50 Gy of RT is the standard CRT regimen for esophageal cancer in the USA.

Several investigators including ourselves also showed promising clinical results using low-dose protracted infusion chemotherapy (CT) combined with full dose RT of 60–66 Gy for locally advanced esophageal squamous cell carcinomas (5–10). A low-dose protracted infusion of 5-FU or 5-FU plus cisplatin was proposed to reduce the acute toxicities due to concurrent CRT (8,10). In addition, to obtain maximum radiosensitization by CT, daily administration of low-dose protracted CT combined with RT may be better than full dose short-term CT plus RT. When this protocol was started, low-dose protracted infusion CT combined with full dose RT of 60–66 Gy was popular for locally advanced esophageal squamous cell carcinomas in Japan (11).

To test the above hypothesis, this randomized Phase II study was conducted to compare the relative toxicity and efficacy of combining full dose short-term CT (arm A) or low-dose protracted CT (arm B) with RT for esophageal cancer (12). The primary endpoint of the study was the 2-year overall survival rate. In the initial report, the 2-year overall survival rates for arms A and B were 46 and 44%, respectively, without significant difference (12). However, the survival curve of arm A was slightly higher than that of arm B after 2 years, with 5-year survival rates of 35 and 24%, respectively. As all patients could be followed up for more than 5 years after randomization, the long-term survival rate and late toxicities of the trial were re-analyzed in this report.

PATIENTS AND METHODS

INVESTIGATIONAL DESIGN

This randomized Phase II multicenter study was started by the Kyoto Radiation Oncology Study Group (KROSG), and joined subsequently by the Japanese Radiation Oncology Study Group (JROSG). The protocol (KROSG0101/JROSG021) was approved by the institutional review boards or ethics committees of all participating institutions, and written informed consent was obtained before entry into the study. The details of the protocol have been published elsewhere (12).

ELIGIBILITY CRITERIA AND TREATMENT PROTOCOL

Inclusion criteria were histologically confirmed esophageal squamous cell carcinoma or adenocarcinoma of Stage II–IVA (UICC 1997). Only patients with no prior therapy, age <75 years, performance status of 0–2, and adequate bone marrow, hepatic and renal function were eligible. Multiple esophageal tumors were also eligible, but tumors with fistula were excluded.

All eligible patients were randomly assigned either to arm A (full dose short-term CT) or arm B (low-dose protracted CT) by customized randomization software; patients were stratified according to tumor length (≤6 vs. >6 cm), clinical stage (Stage IIA, IIB vs. Stage III, IVA) and institution.

Two courses of concurrent CT were combined with RT of 60 Gy/30 fractions/7 weeks (1 week split at the fourth week). A 6–15 MV X-ray was used. The daily fractional dose of RT was 2 Gy administered 5 days a week. The primary tumor and involved lymph nodes of ≥0.5 cm in the shortest diameter on computed tomography represented the gross tumor volume (GTV). The initial 40 Gy was delivered to clinical target volume 1 (CTV1), and the final 20 Gy was delivered to a reduced volume defined as clinical target volume 2 (CTV2) including the GTV with a margin (lateral and anterior/posterior directions 0.5 cm; crano-caudal direction 1 cm). CTV1 for cervical, upper, and middle thoracic esophageal cancer included the GTV with a margin plus the supraclavicular and mediastinal lymph nodal areas (T-shaped field). For cervical esophageal cancer, lower mediastinal lymph nodal areas were excluded from CTV1. For tumors originating in the lower thoracic esophagus, CTV1 included the GTV with a margin plus the mediastinal and perigastric/ celiac lymph nodal areas (I-shaped field).

For both CTV1 and CTV2, a margin (lateral and anterior/posterior directions 0.5 cm; crano-caudal direction 1 cm) was added to make planning target volume 1 and 2 (PTV1,2). In addition, leaf margins for PTV1,2 of 0.5–0.8 mm were added. RT doses were specified in the center of the target volume and calculated with lung inhomogeneity correction.

Two cycles of CT were delivered concurrently with RT for both arms. For arm A, cisplatin 70 mg/m² (Day 1) was delivered via 2 h intravenous infusion (IV), and 5-FU 700 mg/m²/day was administered as a continuous IV (Days 1–5). For arm B, cisplatin 7 mg/m² (Days 1–5 and Days 8–12) was delivered 1 h IV, and 5-FU 250 mg/m²/day was administered as continuous IV (Days 1–14). For arm B, RT was administered within 1 h after the administration of cisplatin. The total dose of CT was the same for the two arms. This schedule was repeated twice every 4 weeks concurrently with RT. For both arms, two cycles of consolidation CT with cisplatin 70 mg/m² (Day 1) and 5-FU 700 mg/m²/day (Days 1–4) were given after CRT as the protocol.

FOLLOW-UP

Locoregional recurrence and distant metastasis were evaluated by barium swallow, upper gastrointestinal endoscopy, and thoraco-abdominal computed tomography scan at
3–6 month intervals after initial evaluation of tumor response. When tumor progression or recurrence was noted, salvage treatment was mandatory for the attending physicians.

Late toxicities observed after 4 months of the start of treatment was graded once a year according to the RTOG/EORTC Late Radiation Morbidity Scoring Scheme and the National Cancer Institute Common Toxicity Criteria (NCI-CTC) (version 2.0), because the CTC for Adverse Events version 3.0 was not available in 2001. Maximum grade scored in the follow-up period was recorded for each patient. Although hypothyroidism was scored once a year, periodical thyroid function tests were not mandatory in the protocol. In terms of secondary malignancy, only malignancies that appeared more than 3 years after the randomization in or near the RT field were recorded.

ENDPOINTS

The primary endpoint of the study was the 2-year overall survival rate. Secondary endpoints were overall survival curves, local control curves, acute and late toxicities and the compliance rate of the protocol. When four cycles of CT and 60 Gy of RT could be given as the protocol, the patient was regarded as being in full compliance with the protocol. When two cycles of CT and 60 Gy of RT could be given concurrently, the patient was regarded as being in partial compliance with the protocol. As the concurrent phase of CRT is a major part of the protocol, when at least two cycles of CT and 60 Gy of RT could be given concurrently (full compliance and partial compliance), patients were regarded as per protocol set.

STATISTICAL ANALYSIS

The probability of survival was estimated using the Kaplan–Meier method with statistical significance assessed by the log-rank test. Data were analyzed according to the intent-to-treat principle. Survival was calculated from the date of randomization. Overall survival considered deaths due to any cause. Local control considered any local or regional tumor progression within CTV1 which received 40 Gy or more. When patients died of distant metastasis or other disease without loco-regional progression, local control was censored. Relationships between hypothyroidism and RT fields or other late toxicities were examined by the χ² test with Yates’ correction.

RESULTS

From December 2001 to June 2006, 91 patients were registered. Forty-six patients were randomly assigned to arm A, and 45 to arm B (Fig. 1). As of June 2011, 71 patients had died, and 20 patients were alive. The follow-up period for the living patients ranged from 59 to 114 months with a median of 83 months. Table 1 shows the characteristics of the 91 patients and treatment parameters according to each treatment arm. There were no significant differences in patient characteristics or treatment parameters between the two arms. The planned dose of 60 Gy was delivered to 88 patients (97%), while RT was terminated at 30 Gy for three patients. When patients with full and partial compliance were combined as per the protocol set, the rate per protocol in arm A (41/46; 89%) was significantly higher than that in arm B (32/45; 71%) (P = 0.031).
All 91 patients were evaluated in terms of survival based on the intent-to-treat principle. Figure 2 shows the overall survival curves for the two arms. The 2- and 5-year survival rates for arm A were 46% [95% confidence interval (CI): 31–59%] and 35% (95% CI: 22–48%), respectively. Those for arm B were 44% (95% CI: 30–58%) and 22% (95% CI: 11–35%), respectively. There was no significant difference between the overall survival curves.

Figure 3 shows the local control curves for both arms. The 2- and 5-year local control rates for arm A were 38% (95% CI: 24–52%) and 30% (95% CI: 17–44%), while those for arm B were 34% (95% CI: 21–48%) and 21% (95% CI: 11–35%), respectively. There were no significant differences between the two curves. When residual or recurrent tumors were detected after 60 Gy of CRT, appropriate treatment was chosen by the attending physicians, and salvage surgery was performed for 16 patients. For 12 patients (6 patients in arm A and 6 in arm B), potentially curative resection was achieved, while non-curative resection was achieved in 4 patients (2 patients in arm A and 2 in arm B).

Late toxicities associated with CRT were scored for 87 patients excluding 4 patients who died within 4 months (Table 2). The follow-up period ranged from 4.5 to 114 months (median; 19.5 months). There were no significant differences in late toxicities between the two arms. Seven (17%) patients in arm A and eight (18%) in arm B showed late toxicities of Grade 3 or more. Most of the toxicities were cardiac or pleural toxicities. Five patients showed Grade 4 toxicities including pericardial effusion, pleural effusion and cardiac infarction. Notably, most patients with severe late toxicities had coexistent hypothyroidism. Table 3 shows the relationship between hypothyroidism and RT fields or other late toxicities in 41 patients who survived more than 24 months.

### Table 2. Late toxicities according to treatment arm [National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0, RTOG/EORTC late radiation morbidity scoring scheme]

<table>
<thead>
<tr>
<th>Arm</th>
<th>A (n = 42)</th>
<th>B (n = 45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophagus G2/3/4</td>
<td>1/1/0</td>
<td>2/1/0</td>
</tr>
<tr>
<td>Heart G2/3/4</td>
<td>0/3/2</td>
<td>2/1/2</td>
</tr>
<tr>
<td>Lung G2/3/4</td>
<td>2/0/0</td>
<td>0/1/0</td>
</tr>
<tr>
<td>Pleura G2/3/4</td>
<td>1/3/1</td>
<td>4/2/0</td>
</tr>
<tr>
<td>Pneumothorax G2/3/4</td>
<td>1/0/0</td>
<td>0/0/0</td>
</tr>
<tr>
<td>Hypothyroid G2/3/4</td>
<td>6/0/0</td>
<td>7/1/0</td>
</tr>
<tr>
<td>Kidney G2/3/4</td>
<td>0/0/0</td>
<td>0/1/0</td>
</tr>
<tr>
<td>Second cancer G2/3/4/5</td>
<td>0/0/1/1</td>
<td>0/0/1/0</td>
</tr>
<tr>
<td>Patient max G2/3/4/5</td>
<td>5/2/4/1</td>
<td>9/5/3/0</td>
</tr>
<tr>
<td>Patient max ≥G3</td>
<td>7 (17%)</td>
<td>8 (18%)</td>
</tr>
</tbody>
</table>

Four patients who died within 4 months were excluded from the analysis of late toxicities.

### Table 3. Relationship between hypothyroidism and RT fields or other late toxicities in patients who survived more than 24 months

<table>
<thead>
<tr>
<th>Hypothyroidism</th>
<th>T-field</th>
<th>I-field</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>Grade 1</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Grade 2–3</td>
<td>13</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other late toxicities</th>
<th>T-field</th>
<th>I-field</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0–1</td>
<td>18</td>
<td>10</td>
</tr>
<tr>
<td>Grade 2–3</td>
<td>0</td>
<td>13</td>
</tr>
</tbody>
</table>

NS, not significant.
more than 24 months. Hypothyroidism of Grade 1–3 was noted in 20 (49%) of the 41 patients. All of the patients with hypothyroidism (Grade 1–3) were treated with a T-shaped field (neck + mediastinum), and no patient treated with an I-shaped field (mediastinum + perigastric/celiac region) showed hypothyroidism ($P < 0.005$). All 13 patients with Grade 2–3 hypothyroidism had coexistent other late toxicities of Grade 2 or more, while only 10 of 28 patients with Grade 0–1 hypothyroidism had other late toxicities of Grade 2 or more ($P < 0.001$).

There were three patients with a secondary malignancy possibly related to cancer treatment. One patient in arm A died of acute myelogenous leukemia 77 months after CRT without recurrence of esophageal cancer (Grade 5). In another patient, follicular lymphoma of the duodenum was detected 53 months after CRT. This tumor occurred out of the perigastric RT field, and was treated successfully with CT. In one other patient, early gastric adenocarcinoma was detected out of the RT field 32 months after CRT. This tumor was resected endoscopically. For this patient, lung squamous cell carcinoma (T1N0M0) was detected 96 months after CRT in the irradiated volume of 20 Gy. Curative surgery was performed for this early lung cancer, and this patient showed no evidence of disease up to 110 months after the CRT. In this patient, gastric cancer was not regarded as a secondary malignancy because of the short interval, but the lung cancer that occurred in the RT field 96 months after CRT was regarded as a secondary malignancy.

**DISCUSSION**

The 5-year minimum follow-up of patients in this analysis is critical for evaluation of long-term survival rates and late toxicities associated with CRT for locally advanced esophageal cancer. Only a few prospective trials on CRT for esophageal cancer reported real long-term survival rates. In the RTOG-8501 trial, the 5-year survival rate of patients treated with 50 Gy CRT was 27% (1,2). In the trial, T4 tumors were not included. In the INT-0123 trial, only overall survival rates within 3 years were reported (4). In the Japan Clinical Oncology Group (JCOG) Phase II study of CRT for resectable esophageal cancer excluding T4 tumors, the 5-year overall survival rate was 37% (13). In arm A, the 5-year overall survival rate was 35% (95% CI: 22–48%), even though 46% of the tumors were T4 disease. Thus, the survival rate in this trial especially for arm A (full dose short-term infusion CT) seems excellent.

In the initial analysis, the survival curve of arm A was slightly higher than that of arm B after 2 years, with 5-year survival rates of 35 and 24%, respectively (12). In the present analysis, the 5-year survival rates were 35 and 22% for arm A and arm B, respectively (Fig. 2). Although the 5-year survival rate was still higher for arm A than for arm B, the difference was not statistically significant. In terms of long-term local control rates, arm A showed a better local control rate than arm B, although this was not significant (Fig. 3). Thus, our initial hypothesis that daily administration of low-dose protracted CT is better than full-dose short-term CT in enhancing radio-sensitization effects was not proved.

Grade 3–5 late toxicities were noted in 17–18% of the patients in this analysis. This rate is much lower than 37% in the 50.4 Gy arm of the INT-0123 or 29% in the CRT arm of RTOG-8501 (2,4). The two trials used the same RTOG morbidity scoring criteria for late toxicities as the present study. Most of the serious late toxicities were cardiac or pleural toxicities, and five patients showed Grade 4 pericardial and/or pleural effusion. Notably, most patients with severe late toxicities had coexistent hypothyroidism. In the present analysis, a significant correlation was noted between Grade 2–3 hypothyroidism and Grade 2 or more other late toxicities (Table 3). Although pericardial and pleural effusion are well-known late toxicities associated with CRT for esophageal cancer (9,13–15), no investigators have described the relationship between hypothyroidism and pericardial and/or pleural effusion. Hypothyroidism was only noted for patients treated with a T-shaped field (neck + mediastinum) after several years of RT, and 14 patients needed thyroid hormone therapy. Hypothyroidism is a well-known late toxicity for head and neck cancer, including cervical esophageal cancer (16–18). However, pericardial and/or pleural effusion are very rare for head and neck cancer. In the treatment of thoracic esophageal cancer, in addition to thyroid glands, the heart and pleura were also irradiated. Thus, the degree of pericardial or pleural effusion may be enhanced by coexistent hypothyroidism.

As a serious late toxicity, secondary malignancies possibly related to cancer treatment were noted in three patients. Although there are several case reports on therapy-related leukemia following definitive CRT for esophageal cancer (19,20), therapy-related solid tumors following CRT for esophageal cancer have not been reported. Acute myelogenous leukemia was noted 77 months after CRT, follicular lymphoma of the duodenum 53 months after CRT and lung squamous cell carcinoma 96 months after CRT. Because a lung tumor was detected 96 months after CRT in the irradiated volume of 20 Gy, the tumor was considered to be a therapy-related tumor. In the present study, two of the three secondary malignancies could be treated curatively. Careful follow-up examinations after 5 years of CRT may be necessary to detect multiple primaries, including CRT-induced secondary malignancies.

In conclusion, our results suggest that low-dose protracted infusion CT with RT is not superior to full-dose short-term infusion CT with RT for esophageal cancer. For long-term survivors after CRT for esophageal cancer, late toxicities including cardiac and pleural toxicities, hypothyroidism and secondary malignancies should be carefully monitored.

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Conflict of interest statement
None declared.

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