Tumor Response after Low-dose Preoperative Radiotherapy Combined with Chemotherapy for Squamous Cell Esophageal Carcinoma

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Abstract. *Aim: Patients with T3 or more squamous cell esophageal cancer underwent low-dose preoperative radiotherapy with chemotherapy, to reduce local recurrence, followed by surgery. The aim was to ascertain tumor response and assess prognostic factors. Patients and Methods: Between May 2002 and June 2011, 37 consecutive patients with esophageal cancer underwent chemoradiotherapy followed by surgery. The numbers of patients in clinical stages IIA/IIIA/IIIB/IIIC were 2/24/7/4, respectively. All were given a dose of 30 Gy in 15 fractions, with concurrent chemotherapy using cisplatin and fluorouracil. Curative surgery was performed a median of 1.2 months after completion of chemoradiotherapy. Results: Based on the findings from surgery, 26 patients (70%) achieved a stage reduction and six patients (16%) had a complete pathological response. The numbers of patients undergoing resections microscopically complete, with microscopically positive margins, and macroscopically positive margins were 33, 3, and 1, respectively. During a median follow-up period of 22.5 months, the two-year progression-free survival and overall survival were 62.1% [95% confidence interval (CI)=45.8 to 78.4%] and 71.9% [95% CI=55.1 to 88.7%], respectively. Statistically significant prognostic factors for overall survival were age [hazard ratio=6.6; 95% CI=1.1 to 38; p=0.04] and pathological T factor [hazard ratio=10.2; 95% CI=1.4 to 77; p=0.02]. No patients died as a result of surgery. Conclusion: Seventy percent of patients with esophageal cancer who received radiotherapy dose of 30 Gy in 15 fractions combined with chemotherapy achieved a stage reduction with low toxicity.*

Esophageal cancer is one of the most fatal types of gastrointestinal cancer. The incidence of esophageal cancer was estimated to be 17,000 in 2007; it is the fourth most frequent gastroenterological cancer in Japan (1). Based on the results of a Japanese randomized trial (2), chemotherapy followed by surgical resection is the main treatment for patients with squamous cell esophageal cancer in Japan. This Japanese study showed a complete response rate of 2.6% after chemotherapy without radiotherapy and locoregional recurrence in a quarter of patients. It has been discussed that more aggressive local therapy, such as radiotherapy to reduce local recurrence, may be preferable.

The addition of radiotherapy to preoperative chemotherapy in order to improve survival has been debated. However, randomized trials comparing chemoradiotherapy followed by surgery with surgery-alone have not demonstrated survival differences (3-5). Meta-analysis studies have compared chemoradiotherapy followed by surgery with surgery-alone and showed survival benefits (6-8) and high postoperative mortality (8) for chemoradiotherapy followed by surgery.

We previously reported the survival benefit for patients with esophageal cancer who underwent preoperative chemoradiotherapy at a dose of 40 Gy in 20 fractions (9). In the present study, we report on patients with T3 or more squamous cell esophageal cancer who were treated with low-dose preoperative radiotherapy of 30 Gy in 15 fractions combined with cisplatin and fluorouracil to enhance the survival benefit and reduce postoperative mortality. Pathological response and local control rates after chemoradiotherapy were retrospectively investigated to determine factors which may contribute to overall survival.

Presented in part at the 54th Annual Scientific Meeting of the American Society for Therapeutic Radiation Oncology (ASTRO), October 28-31, 2012, Boston, MA, U.S.A.

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Key Words: Esophageal carcinoma, chemoradiotherapy, surgery, squamous cell.

Table I. *Patients' characteristics (N=37).*

Median age (range), years		64 (43-77)
Gender	Male:Female	32:5
Performance status	0:1	31:6
cT	T3:T4	34:3
cN	N0:N1:N2:N3	2:26:8:1
Clinical stage+	IIA:IIIA:IIIB:IIIC	2:24:7:4
Tumor location	Cervical:upper:midle:lower	7:5:11:14

+Staged according to TNM Classification of Malignant Tumours seventh edition.

Patients and Methods

Patients. Between May 2002 and June 2011, 37 patients with esophageal cancer underwent chemoradiotherapy followed by surgery at the Tokyo Medical University Hospital and were retrospectively reviewed. All patients who had clinical T3 or T4 esophageal cancer and histologically-proven squamous cell carcinoma included. Patients' characteristics are shown in Table I.

All were staged according to the classification of the Union for International Cancer Control, Seven edition, before chemoradiotherapy using computed tomography (CT), esophagraphy, and esophagogastroduodenoscopy.

Treatment. A total radiation dose of 30 Gy was delivered to all patients in 15 fractions using 3-D multiple-field conformal radiotherapy, with five fractions per week. Chemotherapy was started on the same day as the initiation of radiotherapy. The gross tumor volume (GTV) was defined by the primary tumor and any enlarged regional lymph nodes. The clinical target volume (CTV) was determined by adding 5 cm to the GTV along the esophagus in a vertical direction and 0.5 cm to the GTV around the radial margin. An elective lymph node area was also included in the CTV. Radiation therapy was delivered using a multiple-field technique with photon energy of 10 MV.

A standard chemotherapy regimen, which consisted of a fluorouracil dose of 800 mg/m^2 on days 1 to 4 and a cisplatin dose of 80 mg/m^2 on day 1, was administrered to patients and was repeated every three weeks. If patients had comorbidity, they received a low-dose regimen every four weeks that consisted of a fluorouracil dose of 160 mg/m^2 on days 1 to 5, 8 to 13, and 15 to 22, and a cisplatin dose of 6 mg/m^2 on days 1, 8, and 15.

Four weeks after chemoradiotherapy, all patients underwent thoracic esophagectomy and regional lymphadenectomy. Regional lymph nodes included not only mediastinal (paraesophageal, paratracheal, subcarinal, supradiaphragmatic) and posterior mediastinal lymph nodes, but also perigastric nodes. Dissection of distant lymph nodes, such as cervical nodes or celiac nodes, was optional. The median duration between completion of chemoradiotherapy and surgery was 1.2 months, ranging from 0.9 to 2.3 months. Twenty-six patients underwent three-field dissection and 11 underwent two-field dissection.

Follow-up. During the two years after the completion of treatment, patients were followed up by CT every three months, and then every six months after five years post-treatment. Response to treatment was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria (10). Toxicities were evaluated according to Common Terminology for Adverse Events Criteria, ver. 4 (11).

Table II. *Migration of stage after chemoradiotherapy.*

cStage+ N=37	Number of patients	ypStage+	Number of patients
IIA	2	0, IB	2
IIIA	24	0, IA, IB, IIA	18
		IIIA	2
		IIIB, IIIC	4
IIIB	7	0, IB, IIIA	4
		IIIB	2
		IIIC	1
IIIC	4	0, IB	2
		IIIC	2

+Staged according to TNM Classification of Malignant Tumours seventh edition.

Statistical analysis. Survival was measured from the beginning of radiotherapy using the Kaplan, Meier method, and differences were analyzed with the generalized Wilcoxon test. Progression-free survival was calculated from the date patients began radiotherapy to the date of progression. Infield and local progression-free survival were defined as time to recurrence in the irradiated field and locoregional field, respectively. Cox proportional hazard regression analysis was used to identify the most significant independent prognostic factors. A p-value of 0.05 or less was considered significant. Statistical analysis was performed by SPSS ver. 11 (SPSS Inc., Chicago, IL, USA).

Results

Pathological response. Six patients (16.2%) had a complete response, based on examination of the resected specimens after chemoradiotherapy. Sixteen (43.2%) and 15 patients (40.5%) had a partial response and no response, respectively. The stage migration after chemoradiotherapy is shown in Table II. Twenty-six patients (70.3%) achieved a stage reduction. Thirty-three patients (89.2%) underwent a microscopically-complete resection (R0), while three (8.1%) patients underwent resections with a microscopically-positive margin (R1) and one patient (2.7%) with a macroscopically-positive margin (R2).

Survival. The median follow-up period was 22.5 months. The two- and five-year progression-free survivals were 62.1% (95% confidence interval [CI], 45.8 to 78.4%) and 54.1% (95% CI, 36.5 to 71.7%), respectively. The two- and five-year overall survivals were 71.9% (95% CI, 55.1 to 88.7%) and 62.6% (95% CI, 43.7 to 81.5%), respectively (Figure 1). Overall and progression-free survival were stratified into clinical stage between stages 0-II and stage III, but this did not reach statistical significance (p=0.47 and p=0.31, respectively). Overall and progression-free survival were significantly better in patients with pathological stages 0-II than those with stage III disease (p=0.007 and p=0.03, respectively). Overall survival of patients who achieved a complete response was

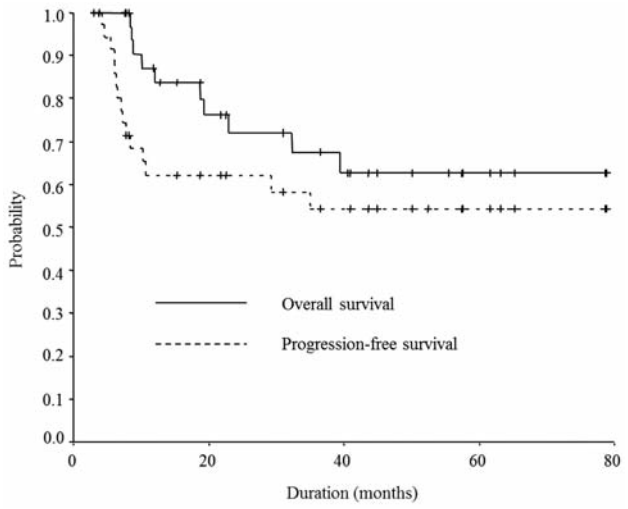

Figure 1. *The Kaplan-Meier curves showing actuarial overall and progression-free survival. The two-year progression-free survival and overall survival were 62.1% [95% confidence interval (CI)=45.8 to 78.4%] and 71.9% (95% CI=55.1 to 88.7%), respectively.*

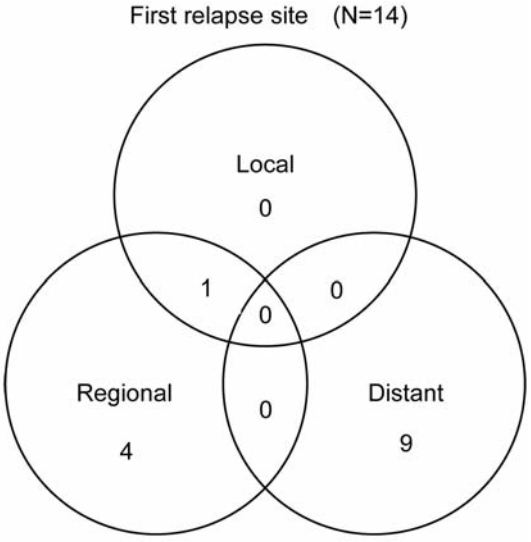

Figure 2. *Fourteen out of the 37 patients experienced disease relapse. Five patients experienced relapse in regional lymph node areas and one had a local synchronous relapse.*

83.3% (95% CI=53.5 to 113%) at five years. Overall survival was statistically significantly longer in patients who underwent R0 resection than those who underwent R1 resection (p=0.01). The two- and five-year overall survival in patients undergoing R0 resection were 75.9% (95% CI=58.9 to 92.9%) and 65.4% (95% CI=45.4 to 85.4%), respectively. The two-year locoregional progression-free survival and in-field progression-free survival were 83.8% (95% CI=70.7 to 96.8%) and 96.6% (95% CI=89.9 to 103.2%), respectively. The statistically significant prognostic factors for overall survival were age (hazard ratio=6.6; 95% CI=1.1 to 38; p=0.04) and pathological T factor (hazard ratio=10.2; 95% CI=1.4 to 77; p=0.02).

First relapse site. One patient suffered from local failure within the regional lymph node. The first relapse sites were at the supraclavicular lymph node for three patients, at the mediastinal lymph node for one patient, and in a distant area that had not been irradiated in nine patients (Figure 2).

Toxicities. Treatment-related toxicities were moderate and included the following: one patient (2.7%) had grade three diarrhea, seven patients (18.9%) had grade two oral mucositis, and six patients (16.2%) had grade two dysphagia. No toxicity caused death related to surgery.

Discussion

A major aim of preoperative radiotherapy is to increase resectability and eradicate residual microcarcinoma, subsequently improving local control and survival. This purpose was achieved based on the low rate of in-field recurrence in our study. Berger *et al*. (12) reported on patients who had a stage reduction to pathological stage 0-I and improved overall survival. They reported the overall survival for patients who had a pathological complete response was 50% at five years. Similarly, in our study, stage reduction and response to chemoradiotherapy were important prognostic factors. Others reported that surgical resectability was another prognostic factor (12-14). In those reports, survival for patients who had R0 resection was 30 to 50% at five years. In our study, the overall survival for patients who underwent R0 resection was 65% at five years.

The reported response rates after treatment with cisplatin-based chemotherapy and concurrent radiation doses of 20 to 60 Gy ranged from 12 to 26% (3, 4, 15-17), with which our results are consistent. Walsh *et al*. (17) and Bosset *et al*. (3) found that adding pre-surgery radiotherapy was a major adverse event that increased perioperative death. In our study, low-dose preoperative radiotherapy of 30 Gy combined with chemotherapy was able to reduce death due to surgery without jeopardizing achieving a high local effect.

Curative radiation doses have recently been investigated preoperatively for patients with esophageal cancer. Tepper *et al*. reported on trimodal therapy (chemoradiotherapy of 50.4 Gy in 28 fractions combined with cisplatin and fluorouracil and surgery) compared with surgery-alone (18). Although this study was closed due to poor accrual, trymodal therapy confirmed significantly improved median survival compared to surgery alone (4.5 *vs*. 1.8 years, p=0.002). In their study, the response rate was 33% for all patients, which consisted of

23% of patients with squamous cell carcinoma patients and 77% with adenocarcinoma. Their article did not report the results for the group of patients with squamous cell carcinoma. However, trymodal therapy appears to be more effective than surgery- alone.

Hagen *et al*. from the Netherlands recently reported the outcome of a randomized trial comparing chemoradiotherapy followed by surgery with surgery-alone (19). The radiation dose was 41.4 Gy given in 23 fractions and the administrered chemotherapy regimen was carboplatin and paclitaxel. The overall survival for patients receiving trymodal therapy was superior to that of surgery-alone. In a subset analysis of patients with squamous cell carcinoma, the response rate was 49%, which was almost twice as high as reported in former studies (3, 4, 15-17) and our study; overall survival in our study was comparable.

The tumor response to induction chemotherapy (20) or chemoradiotherapy (14, 21) was a significant prognostic factor for survival. We reported a predictive method for tumor response after chemoradiotherapy using the proteomic pattern (22). A large-scale study will be necessary to validate this method (23). Studies using the new drug taxane with radiotherapy showed favorable response rates (24-26) compared to using cisplatin and fluorouracil. Ishida *et al*. reported that complete response was achieved in 15% of patients when a relatively high dose of 60 Gy was given in 30 fractions (15). Our data are similar to this. Considerably higher radiation doses, using sophisticated techniques such as proton therapy (27) and intensity modulated radiotherapy (28), or a taxane regimen showed promising results for increasing the tumor response.

Many reports of esophageal carcinoma included adenocarcinoma (29, 30), rather than squamous cell carcinoma, which develops at the gastric and esophageal junction. In contrast, our study only included squamous cell carcinoma of the esophagus. Only one patient had in-field recurrence, but four patients had regional recurrence outside the irradiated volume, which probably indicates inadequate field settings. We expanded the irradiated volume to cover an extensive lymph node region, according to results of a Japanese surgical series (31, 32).

Randomized control trials were performed to investigate induction chemoradiotherapy followed by surgery, or by additional chemoradiotherapy (20, 30). Although higher local failure rates were observed in the additional chemoradiotherapy group, no statistically significant differences were observed between the two groups (33). Preventing local failure appears important in order to maintain quality of life because rescue therapy, including surgery and radiotherapy, is especially difficult for patients with recurrence of esophageal cancer (34). In our study, low-dose preoperative chemoradiotherapy of 30 Gy did reduce death due to surgery without jeopardizing achieving a high local effect. Therefore, we believe this type of trymodal approach is the best choice for patients with T3 or T4 squamous cell carcinoma of the esophagus.

In conclusion, a preoperative low-dose radiotherapy of 30 Gy in 15 fractions combined with chemotherapy achieved stage reduction with low toxicity and low recurrence for 70% of patients with esophageal cancer. This type of trymodal approach appears to be one of the best treatment strategies.

Conflicts of Interest

The Authors declare that they have no conflicts of interest.

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Received January 5, 2013
Revised February 15, 2013
Accepted February 15, 2013