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Efficacy of Neoadjuvant Chemoradiotherapy in Resectable Esophageal Squamous Cell Carcinoma

A Single Institutional Study

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A prospective phase II study of neoadjuvant chemoradiotherapy (CRT) for resectable esophageal squamous cell carcinoma was conducted from May 1993 to March 1996. A total of 88 patients fitted the eligibility criteria and were treated with two courses of induction chemotherapy (cisplatin 60 mg/m^2/day on day 1 and 5-fluorouracil (5-FU) 1 000 mg/m^2/day on days 2–6) with concurrent hyperfractionated radiotherapy (48 Gy/40 fractions/4 weeks) followed by esophagectomy or definitive CRT comprising 4 cycles of cisplatin/5-FU and hyperfractionated radiotherapy (additional 12 Gy) with intracavitary brachytherapy (9 Gy). Clinical response and downstaging were achieved in 83% and 42% of the patients, respectively. With a median follow-up of 77 months, median survival time was 18 months with a 5-year survival rate of 23%. The clinical responses to CRT and surgery were independent prognostic factors for overall survival. Among the intended surgery group ($n = 52$), 41 (79%) patients underwent surgery and 36 had a resection with a pathologic complete response rate of 43%. When compared with a matched historical control ($n = 40$), there was a significant survival benefit in the multimodality arm ($p = 0.04$). This multimodality therapy was feasible and its efficacy was promising, especially when surgical resection was performed. The therapeutic benefit of neoadjuvant CRT remains to be assessed in large well-designed randomized trials, one of which is ongoing at our institution.

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Treatment for patients with esophageal cancer remains unsatisfactory (1). Although surgery alone or chemoradiotherapy (CRT) are generally accepted as reasonable options for patients with locoregional esophageal cancer, the 5-year survival rate with either management is about 20% (2, 3). The actual results of either treatment are probably even worse, as these data are likely to be subject to optimistic selection and publication bias (4). 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 (5–9). 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 (10–15). Nevertheless, the results from phase II and phase III trials at this time are intriguing and serve as an impetus for further investigation of this potential multimodality approach.

We conducted a prospective phase II study of 5-fluorouracil (5-FU)/cisplatin chemotherapy and concurrent hyperfractionated radiotherapy followed by esophagectomy or definitive CRT including intracavitary brachytherapy for locoregional esophageal squamous cell carcinoma. The main objective was to assess overall survival and progression-free survival. We also evaluated treatment toxicity, clinical and pathologic response rate, pattern of failure, and prognostic factors. To evaluate the effectiveness of our treatment regimen, the survival was compared with that of matched historical control patients who had undergone immediate esophagectomy at our institution during the same period.

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MATERIAL AND METHODS

Patients

Patients with previously untreated, biopsy-proven invasive squamous cell carcinoma of the esophagus were eligible for inclusion in the study. Before registration, a multidisciplinary team evaluated each patient to determine potential resectability and operability. Criteria for eligibility included 1) clinically resectable esophageal carcinoma (Stages IIA, IIB and III; T2 ~ 3 N0 M0 and T1 ~ 3 N1 M0 according to the American Joint Committee on Cancer Classification) (16); 2) being older than 18 years; 3) ECOG performance status from 0 to 2; 4) adequate bone marrow reserve consisting of a WBC count of more than 3 500 cells/μL and a platelet count of more than 100 000/μL; 5) adequate renal function with a serum creatinine level of less than 1.5 mg/dL or creatinine clearance of more than 50 mL/min; 6) normal liver function with a serum bilirubin level of less than 1.5 mg/dL; and 7) having no history of prior malignancy, excluding surgically cured basal cell carcinoma of the skin. Although celiac nodes are not considered regional nodes, patients with middle or lower thoracic esophageal cancer with celiac-node enlargement were enrolled because this area was included in the radiation port, and celiac nodes could be resected at surgery.

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 was cervical lymph node involvement or evidence of distant metastasis or if they had previously undergone treatment for esophageal carcinoma. The institutional review board at Asan Medical Center approved the protocol, and informed consent was obtained from the patients.

Pretreatment evaluation

Pretreatment evaluation included a medical history review and detailed physical examination; complete blood cell count with differential; liver function test; creatinine levels and clearance; electrocardiogram; ^{201}Th myocardial perfusion scan or echocardiography; pulmonary function test; chest radiography; barium esophagography; gastrofiberscopy with biopsy; computed tomography (CT) of the chest and upper abdomen; bone scan; and fiberoptic bronchoscopy in cases of upper and middle thoracic esophageal cancer. An experienced radiologist reviewed the CT images and the depth of infiltration and nodal status were classified according to the previously reported methods (17). Endoscopic ultrasonography (EUS) (Olympus EU M3, Olympus Optical Co., Tokyo, Japan) was performed in patients with esophageal wall thickness of less than 10 mm without evidence of mediastinal lymphadenopathy on CT image to exclude stage I (T1N0) disease.

Neoadjuvant chemoradiotherapy and postoperative adjuvant chemotherapy

Neoadjuvant chemotherapy consisted of 2 cycles of cisplatin 60 mg/m^2 by intravenous infusion over 5 h on day 1 and 5-FU 1 000 mg/m^2 daily as a continuous intravenous infusion for 5 days from day 2 to day 6, with an interval of 4 weeks between the first days of each cycle. Radiotherapy was delivered twice a day up to a dose of 48 Gy in 40 fractions of 1.2 Gy with a minimum of 6 h between treatments. The overall treatment time was 4 weeks. Patients underwent simulation by standard methods utilizing esophagoscopy, esophagography and CT. The superior and inferior borders of the field were 7 cm beyond the edges of the carcinoma, whereas the lateral borders of the field were 2 cm beyond the edges. Supraclavicular lymph nodes were routinely encompassed in upper esophageal cancers and celiac nodes in distal or middle esophageal cancers. Radiotherapy was administered with a 15-MV linear accelerator.

From March 1995, the treatment was modified to improve patients' tolerance and compliance: 5-FU was administered for 4 days from day 2 to day 5 with the same daily dose during the first cycle of chemotherapy but omitted during the second cycle of chemotherapy; the second cycle was first given on day 21; the total dose of radiotherapy was also reduced to 45.6 Gy.

Toxic effects were assessed and graded at least once in a week according to the WHO toxicity criteria. Chemotherapy and radiotherapy were withheld if the granulocyte count was less than 1 000 cells/μL or if the platelet count was less than 50 000 cells/μL, and this treatment was not resumed until both the granulocyte and platelet recovered to over 1 500 cells/μL and 7 500 cells/μL, respectively. For grade 3 or worse mucosal toxicity (mucositis or diarrhea), 5-FU was withheld until toxicity resolved, at which point treatment was resumed at 75% of the initial dose. 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 whose oral intake was less than 1 000 Cal/m^2/day due to tumor-induced dysphagia, we preferentially performed the placement of an esophageal stent when the patient began the first cycle of chemotherapy. Enteral and parenteral nutrition were administered as needed.

For patients with disease that was stable or responsive to CRT, 2 cycles of postoperative chemotherapy were begun within 4–6 weeks after surgical resection; 3 cycles of postoperative chemotherapy were administered from March 1995. Each cycle of postoperative chemotherapy was the same as the first cycle of preoperative chemotherapy described above.

Surgical resection

Surgical resection was done 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 $\geq 3\ 500/\mu L$ and platelet count $\geq 100\,000/\mu L$) and no evidence of unresectable disease after repeated chest and abdominal CT scanning. There were no designated surgical procedures for patients in this study. However, the abdominal–cervical approach (transhiatal esophagectomy) was preferentially performed in the first half of the study and then switched to the abdominal–right thoracic approach (Ivor-Lewis) in the second half. Restoration of continuity by esophagogastric anastomosis or colonic interposition with a cervical anastomosis was used. The proximal and distal margins had to be at least 2 cm from the gross tumor. Pathologic examination of a frozen section of the resection margin was performed before completion of the surgery. The celiac axis, periesophageal and subcarinal lymph nodes were routinely sampled during esophagectomy. 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 definitive chemoradiotherapy.

Definitive chemoradiotherapy

For patients who did not want to have surgery from time of registration, who refused surgical resection after preoperative CRT, or were not candidates for surgery owing to poor performance or evidence of disease progression, a second course of CRT was delivered. External beam radiation was given at up to a total dose of 60 Gy using the same fractionation, and additional intraluminal brachytherapy (Ir-198, Nucletron) was delivered at a dose of 9 Gy in 3 fractions. The treatment volume for the second course of external beam radiotherapy was reduced by a 3-cm longitudinal margin and a 2-cm lateral margin from the initial tumor volume. Brachytherapy included initial tumor volume without margins. Chemotherapy consisted of cisplatin and 5-FU using the same dose and schedule for patients with stable disease or disease that was responsive to initial chemoradiation. For patients whose disease progressed during the initial CRT, taxane or mitomycin C-based chemotherapy was given.

Evaluation of response

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

Follow-up evaluation

Follow-up after treatment included visits to medical oncology at 3-month intervals for the first 2 years and every 6 months from the third to the fifth years. During the follow-up visit, patients underwent CT scans and endoscopies every 12 months and whenever clinically indicated. After 5 years, patients were examined annually and radiographic studies were obtained only as clinically indicated.

Statistical analysis

The primary endpoint of this trial was to assess overall survival and progression-free survival. The secondary endpoint was to assess response rate and treatment toxicity. Survival time was defined as the time from the beginning of induction CRT to the time of death due to any cause. Progression-free survival was defined as the time from the start of induction CRT to the first observation of disease progression or death due to any cause. The Kaplan–Meier method was used to calculate median survival rates. Differences in survival with prognostic factors were evaluated by a log-rank test, and Cox's regression models were used to evaluate the joint effect of predictive variables. All statistical comparisons were made with 2-tailed tests, and a p-value < 0.05 was considered as significant.

RESULTS

Patient characteristics

Between May 1993 and March 1996, a total of 111 patients with locoregional esophageal carcinoma were observed at our medical oncology unit. Twenty-three patients were ineligible: 8 patients had clinical T4 tumors (definite bronchial invasion in 2 patients, tracheoesophageal fistula or broncheoesophageal fistula in 5, and left atrial invasion in 1 patient); 5 patients had already undergone some form of treatment of the esophageal tumor; 3 patients had an adenocarcinoma of the esophagus; 4 patients had previous or concomitant malignancies (advanced gastric cancer in 3 and pancreatic cancer in 1); and 3 patients had other medical illness with poor general condition contraindicating chemotherapy and surgery (pulmonary tuberculosis and compromised lung function in 2 patients and lye stricture in 1). Eighty-eight patients fitting all the eligibility criteria were enrolled. Patient characteristics are listed in Table 1. The 13 patients with stage IV disease had celiac-node involvement with no distant metastases.

Clinical response to induction chemoradiotherapy

All but 2 patients completed the CRT program. One patient refused further treatment after the first cycle of CRT, and he

Table 1

Patient characteristics

Characteristics	No. of patients (%)
Total no. of patients	88
Median age, years (range)	63 (42 ~ 81)
Sex (Male/Female)	82/6
ECOG PS	
0, 1	41 (47%)
2	47 (53%)
Anatomic site	
Upper third	8 (9%)
Middle third	33 (38%)
Lower third	39 (44%)
Multifocal or diffuse spreading	8 (9%)
Grade of differentiation	
Well differentiated	15 (18%)
Moderately differentiated	33 (38%)
Poorly differentiated and undifferentiated	20 (23%)
Grade cannot be assessed	20 (23%)
Tumor length	
< 5 cm	32 (36%)
≥ 5 cm	56 (64%)
Median duration of dysphagia, months (range)	2 (0 ~ 9)
Severity of dysphagia	
No dysphagia	12 (14%)
Dysphagia to solid food	42 (48%)
Dysphagia to liquid food	25 (28%)
Dysphagia event to saliva	9 (10%)
Weight loss	
None	29 (33%)
< 10%	47 (53%)
≥ 10%	12 (14%)
Median serum albumin, g/dL (range)	4 (2.7 ~ 5.0)
Clinical stage	
IIA	37 (42%)
IIB	14 (16%)
III	24 (27%)
IV (Celiac LN)	13 (14%)

Abbreviation: LN = lymph node.

underwent delayed esophageal resection at another hospital. The other patient underwent esophageal stent insertion because of aggravating dysphagia after the first cycle of CRT, and then he refused further treatment. Both patients were included for survival analysis. We were able to assess the response to induction CRT in 84 out of 86 patients who completed the planned CRT; one patient died of neutropenic sepsis and multiorgan failure after he completed CRT, and the other patient refused further treatment as well as re-evaluation. Of the 84 patients, the numbers of patients by type of clinical response were as follows: CR, 7 (8%); PR, 64 (76%); SD, 8 (10%); and PD, 5 (6%). Of the 5 patients who had PD, primary tumor progressed in 2 patients (1 histologically confirmed bronchial invasion; 1 thoracic vertebral invasion) and distant metastases developed in 3 patients (1 newly developed para-aortic lymphadenopathy; 1 aggravated celiac lymphadenopathy; and 1 lung metastasis). A comparison of the pre-CRT and post-CRT clinical stage for all patients is presented in Table 2. A total of 35 patients (42%, 95% CI, 31 ~ 51%) were downstaged, while 5 patients (12%) had upstaged disease status after CRT. When we compared the response rates between the original and modified CRT regimens, the response rate was significantly higher for the modified CRT group (79% vs. 92%, $p = 0.03$).

Chemoradiotherapy-induced toxicity

The toxic effects observed during CRT are summarized in Table 3. There was one death related to CRT. The most frequent hematologic toxicity was neutropenia, and the most common non-hematologic toxicities were nausea/vomiting and esophagitis. After we modified the dose of 5-FU and radiotherapy, there was a trend towards a lower incidence of grade 3 or worse toxicities ($p = 0.09$ for esophagitis, $p = 0.12$ for leukocytopenia, and $p = 0.16$ for thrombocytopenia). In patients who received a reduced dose of 5-FU and radiotherapy, surgery was performed 63 ± 18 days after the initiation of CRT, which was a significantly shorter time than that for patients who received the original CRT regimen (77 ± 14 days, $p = 0.01$)

Compliance to surgical resection, pathologic staging and surgical complications

At the time of registration, 52 patients agreed on CRT plus surgery and 36 patients refused surgery and agreed on definitive CRT. Among group intended for surgery, 41 patients (79%) underwent surgery; 18 of 28 patients who had received the original CRT regimen underwent surgery, while 23 of the 24 patients who had received the modified regimen underwent surgery ($p = 0.006$). Surgery was only exploratory in 2 patients because of an intraoperative aortic rupture (described below) in the one and massive bleeding from a malignant ulcer, extending from the distal esophagus to the cardia, in the other. R0 resection was achieved in 36 (88% of 41 patients) patients. A pCR was noted in 17 (43%) of 40 patients in whom pathologic data were available. The pCR rate between the CRT regimens was not different (44% vs. 41%, $p = 0.82$). Of the 36 patients who agreed on

Table 2

Change of clinical stage before and after CRT

Stage		Pre-CRT	Post-CRT*
Stage 0	T0N0	0	7 (8%)
Stage I	T1N0	0	4 (5%)
Stage IIA	T2N0	19 (22%)	20 (24)
	T3N0	18 (21%)	14 (17%)
Stage IIB	T1 or 2N1	14 (16%)	9 (10%)
Stage III	T3N1	24 (27%)	18 (21%)
	T4N0 or 1	0	2 (2%)
Stage IV	M1a/M1b	13 (15%)	10 (11%)
NA		0	4 (5%)

Abbreviations: CRT = chemoradiotherapy; NA = not assessable.
* Downstaged, 35; no change, 44; upstaged, 5.

Table 3

Toxicity of chemoradiotherapy

Type of toxicity	No. of patients (%)*							
	Original CRT regimen (n = 46)				Modified CRT regimen (n = 40)			
	G1	G2	G3	G4	G1	G2	G3	G4
Esophagitis	26	12	4	0	29	8	0	0
Mucositis	13	7	2	0	7	3	0	0
Nausea/vomiting	29	13	2	0	35	5	0	0
Leukocytopenia	11	17	11	2	7	14	3	2
Thrombocytopenia	3	5	2	3	5	3	1	0
Renal toxicity	1	0	0	0	0	0	1	0

Abbreviation: CRT = chemoradiotherapy.
* Toxicity assessment was based on 86 patients who completed neoadjuvant chemoradiotherapy.

definitive CRT, 23 patients completed the scheduled treatment. The accrual and treatment summary is depicted in Fig. 1. Four deaths (10%) were attributed to surgery. One patient died of aortic rupture, which occurred during the dissection of the primary tumor that had fixed firmly to the aorta, and two patients died of pneumonia, sepsis and multiorgan failure within 30 days. Sudden cardiac death occurred in one patient. The most common complication was anastomosis site stricture, which was observed in 9 patients (22%). The surgical details and the complications observed are listed in Table 4.

Survival and prognostic factors

With a median follow-up of 77 months (range, 58 ~ 96 months) for all surviving patients, median survival was 18 months (95% CI, 12 ~ 24 months) with a 1-year survival rate of 68% (95% CI, 58% ~ 78%), 3-year survival rate of 31% (95% CI, 22% ~ 41%), and a 5-year survival rate of 23% (95% CI, 14% ~ 32%, Fig. 2A). Of the clinical parameters tested for association with survival, T stage, ECOG performance status, weight loss, clinical response to CRT, surgical treatment were significant prognostic factors for overall survival (Table 5). A multivariate analysis showed that the clinical response to CRT and surgery were independent prognostic factors for overall survival (Table 6).

For 41 patients who underwent surgery, the median survival was 36 months (95% CI, 13 ~ 58) with a 3-year survival rate of 49% (95% CI, 34 ~ 64) and a 5-year survival rate of 37% (95% CI, 22 ~ 51, Fig. 2B). The survival curve seemed to plateau for the patients who survived more than 5 years. The median survival of the pathologic complete

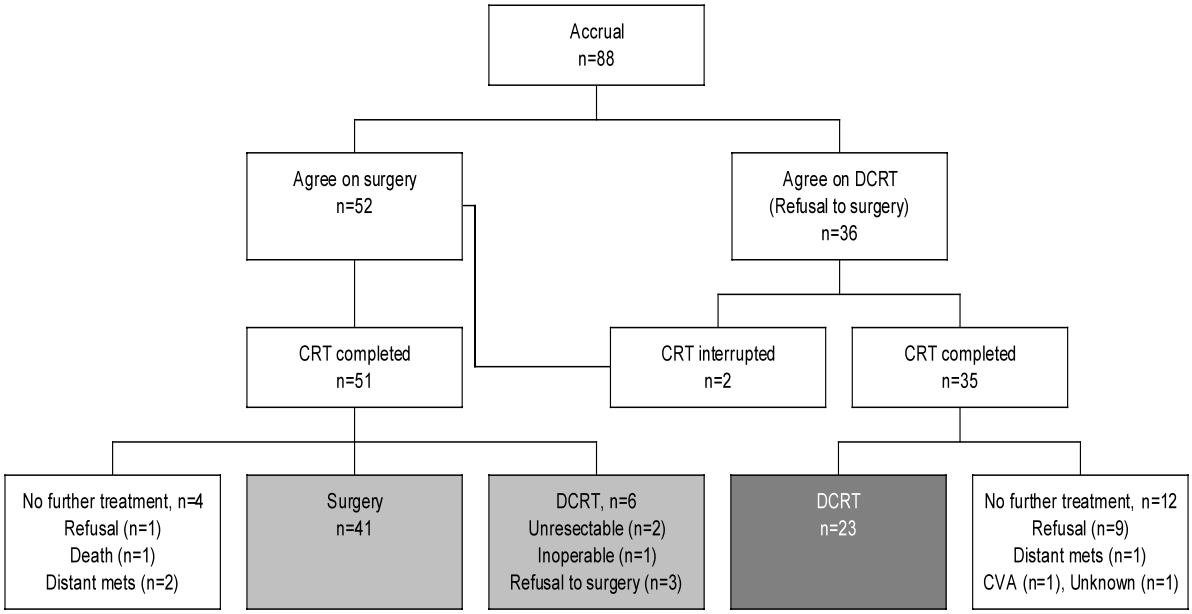

Fig. 1. Accrual and treatment summary. Of 86 patients completing CRT, 41 underwent attempted curative surgical resection, 29 received definitive CRT, and 16 did not receive any further treatment. Abbreviations: CRT = chemoradiotherapy; CVA = cerebrovascular accident; DCRT = definitive chemoradiotherapy.

Table 4

Surgical details

No. of patients enrolled	88
No. of patients agreed on esophagectomy	52
Reasons no surgery undertaken	
Died before surgery	1
Tumor unresectable	4
Patient refused	4
Patient inoperable	1
Incomplete CRT	1
No. of patients received esophagectomy	41
Extent of surgery	
Microscopically complete (R0)	36
Microscopically incomplete (R1)	2
Macroscopically incomplete (R2)	1
Thoracotomy alone	2
Types of esophagectomy	
Transhiatal esophagectomy	28
Ivor–Lewis operation	11
Pathologic staging (available in 40 patients)	
Pathology negative	17
Pathology positive	23
Surgical complications	
Anastomosis stricture	9 (22%)
Wound infection and dehiscence	2 (5%)
Infection other than pneumonia	1 (2%)
Pneumonia, non-life-threatening	2 (5%)
Pneumothorax, long-standing	1 (2%)
Recurrent laryngeal nerve injury	2 (5%)
Sudden cardiac death	1 (2%)
Sepsis and multiorgan failure	2 (5%)
Aortic rupture	1 (2%)

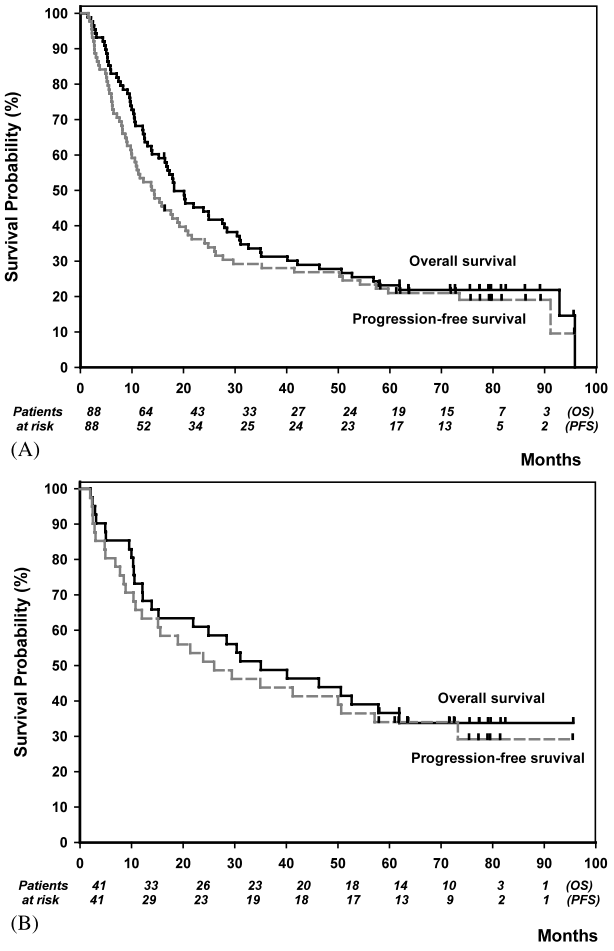

Fig. 2. Overall survival and progression-free survival (A) for all patients enrolled for neoadjuvant chemoradiotherapy followed by surgery or definitive chemoradiotherapy (n = 88) and (B) for patients who underwent surgery after chemoradiotherapy (n = 41).

responders has not been reached. The 5-year survival rate of this group was 59% (95% CI, 35 ~ 82), which was significantly higher than that (20%, 95% CI, 3 ~ 37) of patients with residual viable tumor in the surgical specimen after grossly complete resection (p = 0.002 by the log-rank test, Fig. 3).

Pattern of failure, progression-free survival, and cause of death

Among 51 patients whose tumors developed relapse or progression, 26 (51%) had exclusively locoregional disease, 16 (31%) had distant metastases, and 9 (18%) had both. The median progression-free survival was 14 months (95% CI, 9 ~ 18, Fig. 2A). For the patients who underwent surgery, 39% (16/41) had relapse, which is a significantly lower rate than that for the patients who had a definitive CRT (22/29, 76%, p = 0.002). Taking any locoregional relapse into consideration, 10 (24%) patients who underwent surgery had relapse while 17 (59%) patients who received a definitive CRT had relapse (p = 0.004). No difference was found in the distant metastasis rate between the groups (20% vs. 35%, p = 0.158). Including all the potential clinical factors, we did a bivariate logistic regression analysis to identify the independent factors that could affect the relapse or progression. Attempted surgery was the only statistically significant predictive factor, which favored progression-free status (RR = 0.26, 95% CI, 0.09 ~ 0.81, p = 0.02).

At the time of the analysis, 70 (80%) patients had died. The survival status and causes of death are listed in Table 7. The remaining 5 patients were lost to follow-up: 4 without evidence of disease and 1 with evidence of disease.

Comparison of CRT followed by surgery with surgery alone historical control

For comparison of outcome with intended CRT plus surgery, 40 patients among 168 patients with locoregional esophageal cancer who underwent primary esophagectomy at our institution between February 1990 and June 1996 were selected, matching for age, TNM stage, type of surgery and operation (Table 8). For 52 patients who agreed on surgery at the time of registration (intended CRT plus surgery group), the median survival was 22 months (95% CI, 4 ~ 40) with a 3-year survival rate of 39% (95% CI, 36 ~ 64) and a 5-year survival rate of 29% (95% CI, 17 ~

Table 5

Univariate analysis of potential prognostic factors

Factors		N	Relative risk	p-value	95% CI
Age	< 63 years	40	0.733	0.205	0.453 ~ 1.185
	≥ 63 years	48			
Sex	Female	6	0.694	0.536	0.218 ~ 2.211
	Male	82			
T stage*	T1/T2	35	0.509	0.008	0.306 ~ 0.845
	T3	53			
N stage	N0	42	0.944	0.812	0.586 ~ 1.520
	N1	46			
Tumor length*	< 5 cm	32	0.558	0.024	0.331 ~ 0.942
	≥ 5 cm	56			
ECOG*	0/1	41	0.445	0.002	0.269 ~ 0.735
	2	47			
Weight loss*	None	29	0.608	0.005	0.430 ~ 0.861
	$< 10\%$	46			
	$\geq 10\%$	12			
Clinical response to CRT*	CR/PR	74	0.307	0.001	0.158 ~ 0.599
	SD/PD	12			
Surgery*	Done	41	0.480	0.004	0.292 ~ 0.788
	Not done	47			
CRT regimen	Original regimen	48	1.213	0.430	0.751 ~ 1.959
	Modified regimen	40			

Abbreviation: CRT = chemoradiotherapy.
* $p < 0.05$.

41). There was a statistically significant difference in survival probability between the intended CRT plus surgery group and the surgery alone historical control group ($p = 0.040$ by log-rank test; $p = 0.044$ by Cox's proportional hazard analysis, OR = 0.62, 95% CI, 0.39 ~ 0.98, Fig. 4). In the subset analysis, survival was compared between the patients who underwent surgery after completing CRT ($n = 41$) and the historical control group. The survival probability was significantly better in the patients who underwent surgery after CRT ($p = 0.004$ by log-rank test; $p = 0.005$ by Cox's proportional hazard analysis, OR = 0.48, 95% CI, 0.29 ~ 0.80).

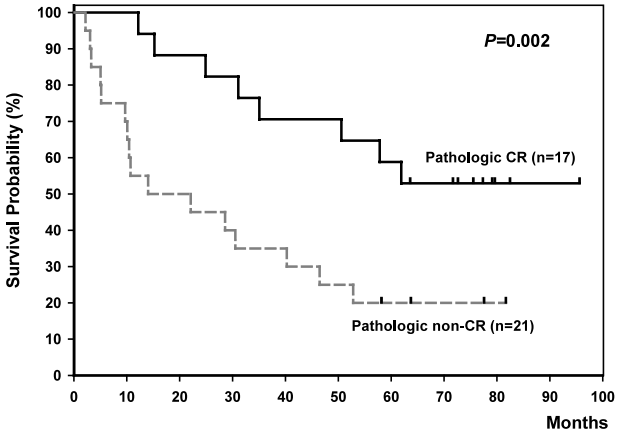

Fig. 3. Overall survival was significantly longer in patients with pathologic complete response (CR) than in patients with R0 resection with residual viable tumors.

DISCUSSION

The rationale for using CRT before surgery includes the elimination of micrometastases and improvement of pri-

Table 6

Cox proportional hazard model for overall survival

Factors		Relative risk	p-value	95% CI
T stage	T1/2 vs. T3	0.625	0.083	0.368 ~ 1.063
Tumor length	< 5 cm vs. ≥ 5 cm	0.636	0.131	0.354 ~ 1.144
ECOG	0/1 vs. 2	0.599	0.083	0.336 ~ 1.069
Weight loss	None vs. $< 10\%$ vs. $\geq 10\%$	0.766	0.173	0.523 ~ 1.124
Clinical response to CRT*	CR/PR vs. SD/PD	0.234	< 0.001	0.112 ~ 0.488
Surgery*	Done vs. Not done	0.517	0.015	0.303 ~ 0.880

Abbreviations: CRT = chemoradiotherapy; CR = complete response; SD = stable disease; PD = disease progression.
* $p < 0.05$.

Table 7

Survival status, sites of first failure, and cause of death

Category	No. of patients (%)
Alive	
Without evidence of relapse or disease progression	12 (14%)
With evidence of disease relapse	1 (1%)
Nature of first relapse	51 (58%)
Locoregional failure	26 (30%)
Distant metastasis	16 (18%)
Local failure and distant metastasis	9 (10%)
Deaths	70 (80%)
Cancer-related	50 (57%)
CRT-related	1 (1%)
Surgery-related	4 (5%)
Secondary primary cancer	5 (6%)
Death from other causes	6 (7%)
Death from unknown cause	4 (5%)

Abbreviation: CRT = chemoradiotherapy.

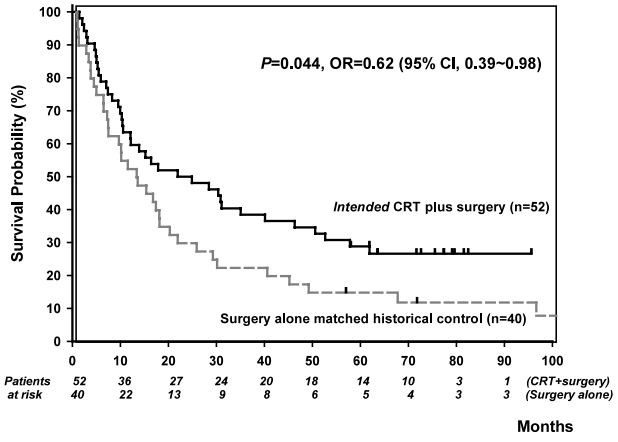

Fig. 4. Comparison of overall survival between intended chemoradiotherapy (CRT) plus surgery vs. a surgery-alone matched historical control.

mary 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 some studies have demonstrated prolonged survival in patients undergoing CRT and esophagectomy compared with historical reports of patients treated with esophagectomy alone (5–9). 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 (10–14, 18). Because of the weaknesses of each study—underpowered inadequate study design; doubtful staging accuracy and stratification; possible unbalanced randomization; variable radiation doses and their delivery; variable chemotherapy regimens; and the relatively poor outcome of the surgery alone group—the true efficacy of induction CRT for esophageal cancer remains unclear and controversial. Nevertheless, the results from phase II and phase III trials at this time are intriguing and lend impetus to further investigation of this potential multimodality approach.

In our study, the combination of 5-FU, cisplatin and hyperfractionated radiotherapy led to a pCR of 43%, which is similar to that of a Swedish multicenter study (46%) (9) and fairly high compared with the results previously obtained with a similar combination using 5-FU and cisplatin (7 ~ 33%) (5, 7, 19–21). Even after we reduced the dose of 5-FU and radiotherapy, the pCR rate remained constant. We used hyperfractionated radiotherapy to deliver 45.6 or 48 Gy in 1.2-Gy twice daily fractions, which is different from other studies. Tumor cell repopulation during CRT is a likely factor contributing to treatment failure, and inefficient radiotherapy fractionation could result in the loss of benefit conferred by the addition of concurrent chemotherapy (3). In order to overcome tumor cell repopulation and reduce preoperative treatment time, hyperfractionation, acceleration, or both have been explored (22,

Table 8

Historical control patients who underwent primary esophagectomy were selected, matching for age, TNM stage, type of surgery, and operators

Matching variables	CRT+Surgery (N = 52)	Surgery Alone (N = 40)	P-value
Age, years, mean (±SD)	60.0±8.6	59.9±8.6	0.94
T Stage*			
T1, 2/T3	24/28(46%/54%)	22/18 (55%/45%)	0.40
N Stage*			
N0/N1	27/25 (52%/48%)	19/21 (48%/52%)	0.67
TNM stage*			
I/IIA/IIB/III	0/27/8/17 (0/52%/15%/33%)	2/17/8/13 (5%/43%/20%/33%)	0.88
Type of surgery			
THE/I-L OP	28/11	27/12	1.00

23). In non-randomized trials of CRT using hyperfractionation encouraging results have been reported (8, 24, 25). Although it has not been shown to be superior to conventional radiotherapy in randomized trial, hyperfractionation radiotherapy and concurrent chemotherapy may be responsible for high pCR rates despite a reduced dose of chemotherapy. In addition, even though there have been conflicting results (1, 21, 26), squamous cell carcinoma is likely to be more sensitive to CRT than adenocarcinoma (18), which perhaps also supports the high pCR rate in our study. In line with previous studies, a pCR to CRT was strongly predictive of long-term survival (5, 6, 9, 14, 15, 20).

In our study, we used strict criteria to assess clinical response. This could be the reason that the clinical CR rate was relatively low compared to other studies and the pCR rate was 5 times the clinical CR rate. Like others, we had difficulties in evaluating the clinical response and the real extent of primary tumor after CRT. CT and gastrofiberscopic examination with biopsy are inaccurate tools for restaging and assessing responses to CRT because it is difficult to differentiate post-CRT inflammation/fibrosis from residual viable cancer (27). Even EUS and positron emission tomography (PET) have limited value in accurately assessing pathologic stage after neoadjuvant CRT (28–30). In this study, 24 out of 41 patients who underwent esophagectomy after CRT were assessed by EUS before resection and the accuracy of EUS for response assessment was relatively poor (data not shown). One of main reasons for poor accuracy was reactive lymph node hyperplasia after CRT.

Although there was one CRT-related death, which occurred in a patient who received the original CRT regimen, CRT was generally well tolerated, especially when the doses of RT and 5-FU were reduced, and allowed a complete surgical resection (93%) without technical difficulties. There were four postoperative deaths (10%). Although this figure is rather high for a modern series (9, 14), it was comparable to that observed with the surgery alone matched historic control and that of reports elsewhere (2, 8, 10–13, 31). These findings confirm that preoperative regimens have not led to an increase in postoperative mortality and morbidity (12, 18, 31).

The 3-year survival rate for the entire patient population was 31%, which is better than or similar to that obtained in similar studies (9, 11–14). For patients who agreed on CRT plus surgery, the 3-year survival rate was 39%, which was superior to that of other well-known phase III studies (10–14) and similar to that of previous phase II studies (5, 6, 32). The survival advantage of this combined modality therapy after 5 years seems durable. Although Bidoli et al. (33) reported that cumulative survival continued to fall after 5 years, this fact was drawn from fewer than 10 patients, and these researchers did not comment on the cause of death after 5 years. Whether the survival curve had reached its plateau at 5 years, and thereby it is equivalent to cure, requires continued follow-up.

We compared the results achieved by the patients who agreed on CRT followed by surgery with those of the historical control patients who received surgery alone. One potential bias was that the CRT group was likely to do better than the control group, as survival and outcomes have improved over time because of improved surgical skills and perioperative intensive care management. Although this historical control group of patients was operated on in the era before we started our phase II trial, they were operated on by the same surgical team and selected for surgical exploration on the basis of more strict operability criteria (exclusion of patients with celiac lymph node enlargement). In addition, the demographic characteristics, the distribution of disease stage, and operation type were comparable. It is conceivable that this historical group could serve as a baseline comparison model for our phase II trial. The survival curves for the CRT plus surgery group and surgery alone matched historical control (Fig. 4) are relatively indistinguishable until 5 to 10 months after the initiation of the treatment, when two curves begin to diverge; this might mean that perioperative and intensive care management did not confound the overall results. The 3-year survival rate for the historical control group was 23%, which is somewhat higher than would be expected from the previous phase III studies (10, 12–14). Although the matched historic control may be systematically different from the CRT group in some unknown and unmeasurable ways, the significant survival advantage for the CRT plus surgery group led us to investigate the randomized phase III trial.

In this study, the patients who received surgery after CRT had fewer relapses ($p = 0.002$) and fewer local recurrences ($p = 0.004$) compared with those who received definitive CRT. These findings reinforce the need for additional esophagectomy for disease control and long-term survival (34). In several studies on the treatment of locoregional esophageal cancer with CRT alone, high locoregional failure rates have been reported (33, 35–37). The effect of this poor locoregional control on the development of disseminated metastatic disease and long-term survival is still unknown but it certainly can contribute to poor quality of life and subsequent death. Although not statistically significant, patients who received CRT plus surgery had fewer distant metastases than those who received definitive CRT. Recently, the EORTC reported (in abstract form) an early result from a randomized trial (FFCD 9120) on CRT followed by surgery versus definitive CRT. In that trial, surgery did not result in an additional survival benefit to the patients with advanced operable esophageal cancer responding to CRT (38). Nonetheless, we are still waiting for the final results before we can draw any conclusions. Surgical resection may remain an integral component of

multimodality treatment in resectable esophageal cancer until CRT alone can achieve a high locoregional control rate (4, 34).

Our 5-FU/cisplatin chemotherapeutic regimen could be criticized as being outdated and suboptimal in the light of newer agents, such as taxane, irinotecan, gemcitabine and monoclonal antibodies, which are being explored for their efficacy (1). However, several phase II trials using these newer agents and radiotherapy have reported a pCR rate of about 20% as a surrogate endpoint, and the survival outcomes have not been sufficiently promising with higher toxicities (39–42).

In conclusion, improved long-term survival was obtained in patients with locoregional esophageal squamous cell carcinoma using neoadjuvant chemotherapy with concurrent hyperfractionated radiotherapy followed by surgery. The high CR rate with acceptable morbidity has made neoadjuvant CRT the gold standard for treatment of resectable esophageal cancer at our institution. The therapeutic benefit of CRT and esophagectomy over esophagectomy alone remains to be assessed in large well-designed phase III trials, one of which is ongoing at our institution.

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