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ORIGINAL ARTICLE

Phase II study of use of a single cycle of induction chemotherapy and concurrent chemoradiotherapy containing capecitabine/cisplatin followed by surgery for patients with resectable esophageal squamous cell carcinoma: long-term follow-up data

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Abstract
Purpose This phase II study evaluated the feasibility and efficacy of one cycle of induction chemotherapy, followed by concurrent chemoradiotherapy (CRT) featuring capecitabine/cisplatin, followed in turn by surgery, in the treatment of patients with resectable esophageal squamous cell carcinoma.
Methods Between March 2003 and April 2005, 54 patients with stage II or III esophageal cancer were treated with induction chemotherapy (cisplatin 60 mg/m^2 on day 1; capecitabine 1,000 mg/m^2 bid on days 1–14) followed by concurrent radiotherapy (46 Gy in 23 fractions) and chemotherapy (cisplatin 30 mg/m^2 on days 1, 8, 15, and 22; capecitabine 800 mg/m^2 bid 5 days/week). Surgery was performed within 8 weeks of the end of radiotherapy.
Results Median age of the patients was 64.5 years (range, 45–74 years). After CRT, 52 patients (96%) showed a clinical response, including 26 (48%) who exhibited a complete response (CR). Surgery was performed on 41 patients (76%), with 20 (37%) achieving pathologic CR and 3 (6%) dying of postoperative pneumonia. At a median follow-up time of 74.2 months (range, 64.3–84.8 months), 16 patients (30%) had experienced tumor recurrence and 36 (67%) had died. Of the 41 patients who underwent esophagectomy, 5 (12%) had exclusively locoregional disease and 7 (17%) had distant metastasis, whereas no one had both. The 5-year progression-free and overall survival rates were 30.2% (95% confidence interval [CI], 18.0–42.4%) and 37.0% (95% CI, 24.1–50.0%), respectively.
Conclusions A trimodal approach, consisting of a single cycle of induction chemotherapy, CRT containing capecitabine and cisplatin, and surgery, was feasible and effective in patients with resectable esophageal squamous cell carcinoma.

Keywords Esophageal neoplasm · Squamous cell carcinoma · Combined modality therapy · Phase II clinical trial · Survival

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Introduction

Although about 30–50% of patients with esophageal cancer have resectable disease, the 5-year survival rate of resected

patients remains poor (20%) because of high rates of local recurrence and distant metastasis [1, 2]. Preoperative local and systemic treatment modalities, including preoperative concurrent chemoradiotherapy (CCRT), have been shown to improve treatment outcomes [3, 4]. Although randomized trials have yielded conflicting results, because of statistical underpowering and inadequate study design [5–9], a recent meta-analysis reported that preoperative CCRT enhanced 2-year survival rates by 13% compared with surgery alone [10].

Our center has administered preoperative CCRT to patients with locoregional esophageal cancer in the interval since 1993 [11]. A phase II study of preoperative CCRT containing 5-fluorouracil (5-FU)/cisplatin followed by esophagectomy showed promising results, with a median survival time of 22 months and a pathologic complete response (pCR) rate of 43% [12]. We therefore initiated a phase III study comparing preoperative chemoradiotherapy followed by surgery with surgery alone for patients with resectable esophageal squamous cell carcinoma [13]. Although an interim analysis revealed no significant difference in survival, and per-protocol analysis favored preoperative CCRT, the trial was discontinued because of an unexpectedly high drop-out rate (31%) prior to esophagectomy.

The oral fluoropyrimidine capecitabine (Xeloda®) is a prodrug designed to preferentially generate 5-FU in tumor tissues and to mimic continuous infusion of 5-FU [14]. The ease of administration and tolerable toxicity profile have rendered concurrent capecitabine and radiation therapy an attractive option in the treatment for metastatic gastrointestinal malignancies [15]. Capecitabine and cisplatin have been shown to be active and well tolerated as first-line treatment of patients with recurrent or metastatic esophageal carcinoma [16, 17]. In addition, induction chemotherapy prior to preoperative CCRT has been shown to improve tumor response and survival outcomes [18, 19]. We therefore conducted a prospective phase II trial consisting of one cycle of induction chemotherapy, concurrent CCRT containing capecitabine/cisplatin, and surgery for patients with resectable esophageal squamous cell carcinoma.

Materials and methods

Patients

Patients with previously untreated, biopsy-confirmed invasive squamous cell carcinoma (SCC) of the esophagus were eligible. Before enrollment, a multidisciplinary team (Esophageal Cancer Study Group, ECSG) at the Asan Medical Center (Seoul, Korea) evaluated each patient to determine potential resectability and operability. Patients were considered eligible if they had clinically resectable esophageal carcinoma (stage IIA, IIB, or III; grade T2–3N0M0 or T1–3N1M0 according to the AJCC, 6th edition); age $\geq$18 and $\leq$75 years; Eastern Cooperative Oncology Group (ECOG) performance status (PS) $\leq$ 2; adequate bone marrow reserve (white blood cell [WBC] count $>$3,500 cells/μl and platelet count $>$100,000/μl); adequate renal function (serum creatinine $<$1.5 mg/dl or creatinine clearance $>$50 ml/min); normal liver function with serum bilirubin concentration $<$1.5 mg/dl; and no history of prior malignancy. Patients were ineligible if the primary tumor was located in the cervical esophagus (upper border $<$18 cm from the incisor teeth), if celiac or para-aortic lymph node involvement was evident, if tracheobronchial infiltration was present, if laryngeal nerve palsy or evidence of distant metastasis was noted, or if prior treatment for esophageal carcinoma had been administered. The institutional review board at the Asan Medical Center approved the protocol, and each patient provided written informed consent.

Pretreatment evaluation

Pretreatment evaluation in patients with upper and middle thoracic esophageal cancer included a medical history review and a detailed physical examination, assessment of ECOG PS, complete differential blood cell count, liver function tests, measurement of creatinine concentration and clearance, electrocardiography, [^{201}]thallium myocardial perfusion scanning or echocardiography, a pulmonary function test, chest radiography, barium esophagography, gastrofiberoscopy with biopsy, endoscopic ultrasonography (EUS), computed tomography (CT) of the chest and upper abdomen, bone scanning or positron emission tomography (PET), and fiberoptic bronchoscopy.

Induction chemotherapy and concurrent chemoradiotherapy

Patients received one cycle of induction chemotherapy, consisting of an intravenous (i.v.) infusion of cisplatin 60 mg/m^2 on day 1 and capecitabine 1,000 mg/m^2 bid daily for 14 days. This was followed 3 weeks later by three-dimensional conformal radiotherapy, consisting of 46 Gy in 23 fractions (2 Gy per fraction per day), and concurrent administration of cisplatin 30 mg/m^2 once weekly and capecitabine 800 mg/m^2 bid 5 days per week until the end of radiotherapy. The gross target volume (GTV) for three-dimensional conformal radiotherapy was determined from PET and chest CT results. The clinical target volume (CTV) included the mediastinum and esophagus within a cephalocaudal margin 5 cm from the GTV. If the GTV was located above the carina or the clinical stage was T3-T4 or N1, the supraclavicular fossa was included. When the supraclavicular fossa was

irradiated, we used a cervical midline block at the outside of the PTV to preserve the anastomosis and spinal cord. If the esophagogastric junction was within 5 cm of the GTV inferiorly, the celiac trunk was included.

Toxicity was assessed at least once per week and graded according to the National Cancer Institute-Common Toxicity Criteria [NCI-CTC] version 2.0. Chemotherapy and radiotherapy were withheld if the granulocyte count was <1,000 cells/μl or if the platelet count was <50,000 cells/μl, and neither treatment was resumed until both measures recovered to >1,500 and 75,000 cells/μl, respectively. Cisplatin was withheld in patients with grade ≥2 renal toxicity until the creatinine concentration had recovered to 1.5 mg/dl, at which point cisplatin was resumed at 50% of the initial dose. Esophageal stents were inserted at the start of chemotherapy in patients with cancer-induced dysphagia, who could not consume a soft diet. Patients with oral intake <1,000 Cal/m^2/day during treatment were recommended for enteral and parenteral nutrition.

Surgical resection was performed within 8 weeks after the end of radiotherapy. Patients who underwent surgery were required to show adequate bone marrow recovery (WBC count 3,500/μl and platelet count ≥100,000/μl) and to have no evidence of unresectable disease on repeated chest and abdominal CT scans.

Surgical resection

Tumors were resected using an abdominal–right thoracic approach (Ivor Lewis) or a right thoracic–abdominal–cervical approach (McKeown), with two- or three-field lymph node dissection, respectively. The proximal and distal margins were at least 6–8 cm from the gross tumor. Tissue samples were examined by a dedicated pathologist, with resections classified as complete when all gross tumor tissue had been removed and microscopic examination revealed that all margins were free of tumor (R0). Resections were considered incomplete when microscopic examination revealed positive margins (R1) or residual gross disease (R2). Patients in whom surgical resection was incomplete were treated with additive postoperative radiotherapy, with or without chemotherapy.

Evaluation of response after CCRT

Following preoperative treatment, all patients were evaluated endoscopically by biopsy and by EUS, CT, and/or PET. Endoscopy, CT, and PET were performed again 3–4 weeks after the end of radiotherapy. Patients with no radiographic or sonographic evidence of disease and no residual tumor as revealed by esophagoscopy and who were biopsy-negative were defined as achieving a complete response (CR). Otherwise, the response was classified as improved (because of difficulties in defining a partial response), or patients were considered to have stable disease (SD) or to show disease progression (PD). A complete pathologic response (pCR) after surgical resection was defined as the absence of residual tumor in the esophagus and lymph nodes.

Follow-up evaluation and assessment of endpoints

Follow-up included a visit to the medical oncology clinic every 3 months for the first 2 years and every 6 months thereafter. Patients were assessed by CT scans and endoscopy every 12 months and whenever clinically indicated.

Statistical analysis

The primary endpoint of this phase II trial was pCR rate; secondary endpoints included clinical response, the extent of toxicity, progression-free survival (PFS), and overall survival (OS). OS was calculated from the date of induction chemotherapy to the date of death from any cause. PFS was defined as the interval from the date of induction chemotherapy to the date of first observation of progression, recurrence, or death from any cause. Survival was evaluated by the Kaplan–Meier method. Univariate analyses of the effects of covariates on survival were analyzed using the log-rank test. Cox's proportional hazards model and logistic regression were used in multivariate analysis.

We employed the Simon two-stage minimax design to calculate sample size. The maximum clinical response rate (RR) was 30% (P0), and the minimum RR that was considered to be of interest was 50% (P1). To detect such a difference, we required a minimum of 39 patients (two-sided test; type I error 5% and power 80%). Such a design minimizes the required number of treated patients if the response rate is inadequate. If six or fewer responses had been observed in the first 19 patients, the study would have been terminated. If responses had been noted in 7 or more of the 19 patients, 20 additional patients would have been enrolled. If ≤16 responses had been observed among these 39 patients, the study would be considered inadequately powered, whereas if ≥17 responses were observed, treatment would be declared effective. Assuming a 25% drop-out rate prior to surgery, we planned to enroll 50 patients**.** All tests of significance were two-sided, and differences were considered statistically significant at $P < 0.05$.

Results

Patient characteristics

Between March 2003 and April 2005, 54 patients fulfilled the eligibility criteria and were enrolled (Fig. 1).

Pretreatment characteristics are summarized in Table 1. Forty-eight patients (89%) were men, and the median age of all patients was 64.5 years (range, 45–74 years). Eleven patients (20%) had an ECOG PS 0 score (asymptomatic), whereas 30 (55%) had tumors located in the lower third of the esophagus. Before treatment, 8 (15%) had stage IIA, 15 (28%) stage IIB, and 31 (57%) stage III tumors.

Clinical response and toxicity of chemoradiotherapy

Fifty-two patients (96.3%) completed the planned CCRT. The other two patients received incomplete CCRT because of poor general condition; however, one eventually underwent surgery. By the end of induction chemotherapy and CCRT, patients had received an average relative dose intensity (RDI) of capecitabine of 92.4% (range, 34.7–100.0%) and an average cisplatin RDI of 100%. Of the 54 patients evaluated in terms of clinical response at the end of CCRT, 26 (48%) had achieved CR, 26 (48%) had improved, and 2 (4%) showed PD, giving an overall clinical response rate of 96% (95% CI, 91–100%). Of the 44 patients who underwent endoscopic biopsy, 42 (95%) had achieved CR and 2 (5%) had residual lesions. Toxicities observed during CCRT are summarized in Table 2. There were no deaths related to CCRT. The most common hematologic toxicity was neutropenia, and the most common non-hematologic toxicities were esophagitis and nausea/vomiting.

Compliance with surgical resection, pathologic staging, and surgical complications

At the time of registration, all patients agreed to undergo surgery after CCRT; however, 12 patients subsequently refused surgery, because of symptomatic improvement ($n = 8$), poor condition ($n = 2$), or tumor progression ($n = 2$). Therefore, 42 patients underwent surgery. By intention-to-treat analysis, 40 patients (74%) underwent R0 or complete resection, including 34 who underwent Ivor Lewis operations and 6 who received McKeown operations. One patient underwent a transhiatal esophagectomy because of the presence of comorbidities, including liver cirrhosis, thrombocytopenia, and chronic empyema caused by tuberculosis. Another patient underwent palliative jejunostomy because of aortic invasion, although he was assessed as improved after CCRT. The median number of lymph nodes dissected per patient was 42 (range, 14–71). We found that 20 patients (37%) achieved pCR and 21 had residual lesions. Three patients (6%), all of whom achieved pCR, died within 30 days after esophagectomy because of postoperative pneumonia and multi-organ failure. Surgical details and complications are summarized in Table 3.

Patterns of recurrence and survival

At a median follow-up time of 74.2 months (range, 64.3–84.8 months), 16 patients (30%) had experienced tumor recurrence and 36 (67%) had died; the causes of death were disease-related in 21 patients; treatment-related in 5; and attributable to other causes in 10, including pneumonia in 6, tuberculosis in 1, and unknown reasons in 3. Of the 41 patients who underwent esophagectomy, 5 (12%) had exclusively locoregional disease and 7 (17%) had distant metastases, whereas no one had both. Sites of distant recurrence included the lungs/pleural effusion ($n = 5$), pericardial effusion ($n = 3$), liver ($n = 1$), and intra-abdominal lymph node ($n = 1$), with three patients having multiple metastases. Of the 13 patients who did not undergo esophagectomy, 2 (15%) experienced local recurrence and 2 (15%) had distant metastases.

The median PFS and OS of the 54 patients were 20.0 months (95% CI, 9.4–30.7 months) and 34.1 months

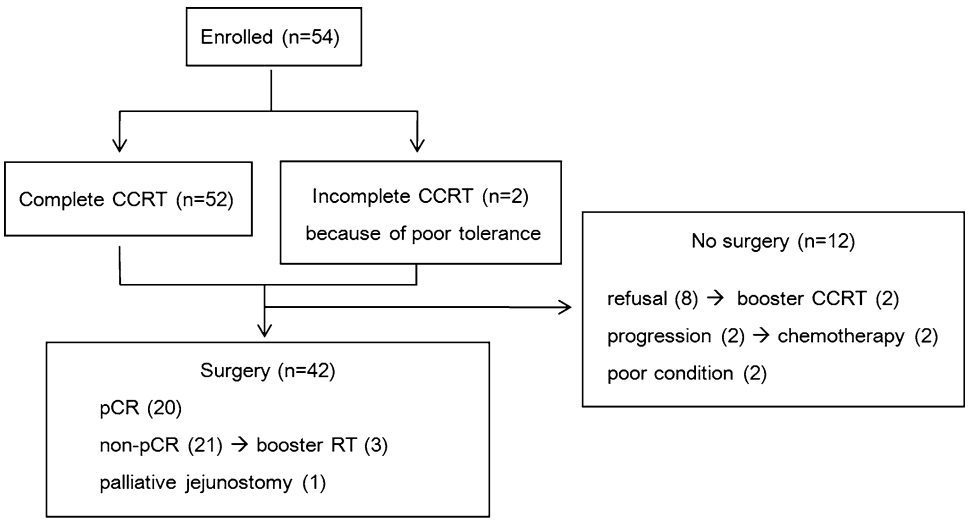

Fig. 1 Study scheme. *CCRT* concurrent chemoradiotherapy, *pCR* pathologic complete response, *RT* radiotherapy

Table 1 Patients' characteristics (total = 54)

		No. of patients (%)
Age (years)	Median (range)	64.5 (45–74)
Gender	Male	48 (88.9%)
ECOG, PS	0	11 (20.4%)
	1	43 (79.6%)
Tumor location	Upper 1/3	3 (5.6%)
	Middle 1/3	21 (38.9%)
	Lower 1/3	30 (55.5%)
Histology	WD	6 (11.1%)
	MD	38 (70.4%)
	PD	10 (18.5%)
Tumor diameter	<5 cm	31 (57.4%)
	≥5 cm	23 (42.6%)
Dysphagia	Median duration (months)	1.7 (0–7)
Severity of dysphagia	No dysphagia	13 (24.1%)
	Dysphagia to solid food	22 (40.7%)
	Dysphagia to liquid food	19 (35.2%)
Weight loss (over 3 months)	None	33 (61.1%)
	<10%	18 (33.3%)
	≥10%	3 (6.6%)
Albumin	Median (mg/dl, range)	3.9 (3.3–4.8)
Clinical stage	IIA/B	23 (42.6%)
	III	31 (57.4%)

ECOG PS Eastern Cooperative Oncology Group Performance Status, *WD* well differentiated, *MD* moderately differentiated, *PD* poorly differentiated

(95% CI, 11.2–56.9 months), respectively (Fig. 2). The 3-year and 5-year PFS rates were 40.1% (95% CI, 27.0–53.2%) and 30.2% (95% CI, 18.0–42.4%), respectively, whereas the 3-year and 5-year OS rates were 50.0% (95% CI, 36.7–63.3%) and 37.0% (95% CI, 24.1–50.0%), respectively. Per-protocol analysis of patients who did ($n = 41$) and did not ($n = 13$) undergo esophagectomy, including one who underwent palliative jejunostomy, showed that median PFS (27.4 months, 95% CI, 10.8–44.0 months vs. 6.5 months, 95% CI, 0.0–14.7 months; $P = 0.060$) and OS (38.4 months, 95% CI, 1.0–75.8 months vs. 14.2 months, 95% CI, 0.0-31.9 months; $P = 0.216$; Fig. 3) tended to be higher in the former group. In addition, survival was found to plateau after 5 years; the 7-year PFS (30.2, 95% CI, 18.0–42.4%) and OS (30.2, 95% CI, 18.0–42.4%) values did not rise further in the absence of secondary development of primary cancer.

Univariate and multivariate analyses and prognostic factors

By univariate analysis, ECOG PS and clinical response were significantly associated with PFS, whereas only clinical response was significantly associated with OS (Table 4). Multivariate analysis showed that ECOG PS was independently associated with PFS and gender was independently associated with OS (Table 5). Clinical response showed a borderline association with both PFS ($P = 0.058$) and OS ($P = 0.052$).

Discussion

This phase II trial of a single cycle of induction chemotherapy, followed by CCRT containing capecitabine and cisplatin, in turn followed by surgery, demonstrated reasonable short-term results with a curative resection rate of 74%, a pCR rate of 37%, and a clinical CR rate of 48%. Moreover, long-term follow-up confirmed that outcomes were favorable, with 5-year PFS and OS rates of 30 and 37%, respectively. Although all of treatment schedule, the optimal delivery of chemo- and radiotherapy, and the chemotherapeutic agents of choice remain to be standardized, a combination of 5-FU and cisplatin has become a well-regarded treatment for CCRT both because of minimal cytotoxic effects and because of the fact that the regime serves as a radiosensitizer [20]. A combination of capecitabine and cisplatin has antitumor and radiosensitizing activities similar to those of 5-FU plus cisplatin [15]. Capecitabine, which is taken orally, is more convenient for

Table 2 Toxicities associated with chemoradiotherapy

	No. of patients (%)			
	Grade 1	Grade 2	Grade 3	Grade 4
Neutropenia	15 (27.8%)	15 (27.8%)	8 (14.8%)	0
Thrombocytopenia	27 (50.0%)	7 (13.0%)	4 (7.4%)	0
Esophagitis	35 (64.8%)	5 (9.2%)	0	0
Nausea/vomiting	29 (53.7%)	8 (14.8%)	1 (1.8%)	0
HFS	3 (5.6%)	0	0	0
Nephrotoxicity	1 (1.8%)	0	0	0
Elevated AST/ALT	1 (1.8%)	0	0	0

HFS hand-foot syndrome, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase

Table 3 Surgical details and complications

Number of patients	54 (100.0%)
Reasons surgery not performed	12 (22.2%)
Patient refusal	8 (14.8%)
Progression	2 (3.7%)
Poor condition	2 (3.7%)
Type of esophagectomy	42 (100.0%)
Ivor Lewis operation	34 (81.0%)
McKeown operation	6 (14.2%)
Transhiatal esophagectomy	1 (2.4%)
Open and closure	1 (2.4%)
Median number of lymph nodes dissected	42 (range, 14–71)
Pathologic status	41 (100.0%)
Negative (complete response, pCR)	20 (48.8%)
Positive (residual disease)	21 (51.2%)
Surgical complications	41 (100.0%)
Anastomosis-site stricture	1 (2.4%)
Pneumothorax, long standing	1 (2.4%)
Wound infection	1 (2.4%)
Pneumonia, non-life-threatening	2 (4.9%)
Infection other than pneumonia	1 (2.4%)
Pleural effusion, long standing	3 (7.3%)
Sepsis and multi-organ failure	3 (7.3%)

patients and may be prescribed in an outpatient setting, thus improving patient compliance. We found that capecitabine/cisplatin plus 46 Gy of radiation resulted in pCR, PFS, and OS outcomes similar to those reported in other trials of trimodal treatment in patients with resectable esophageal carcinoma [5, 7, 21]. The toxicities associated with preoperative CCRT were acceptable and manageable,

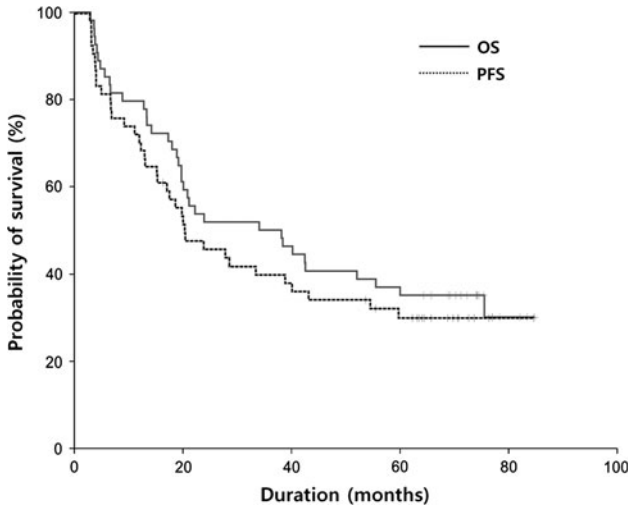

Fig. 2 Kaplan–Meier analysis of progression-free survival (PFS) and overall survival (OS) in 54 patients with esophageal squamous cell carcinoma

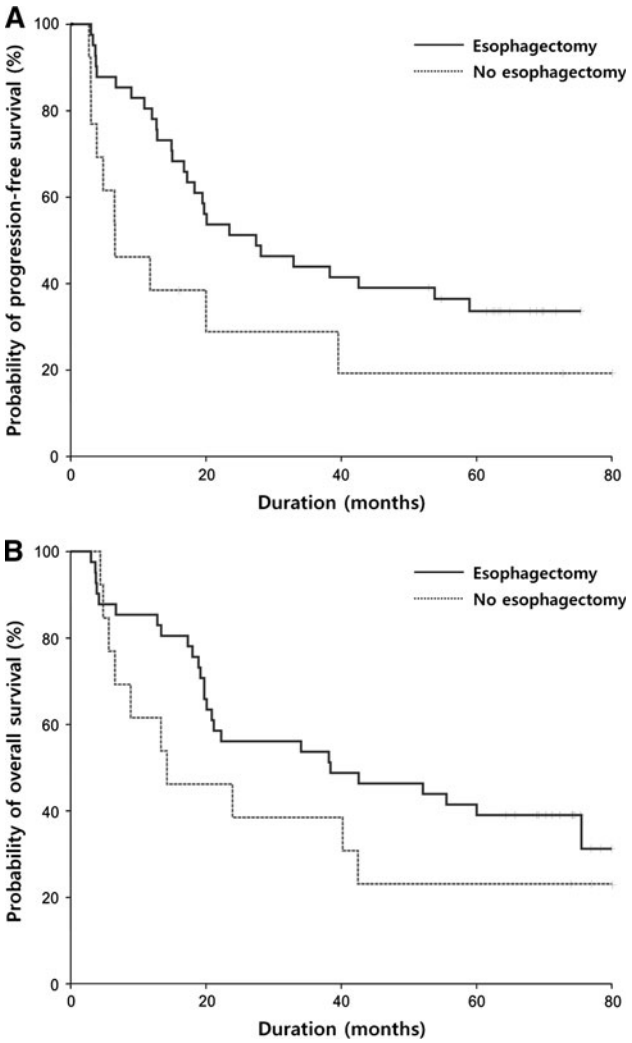

Fig. 3 Kaplan–Meier analysis of (**a**) progression-free survival (PFS) and (**b**) overall survival (OS) of patients who did and did not undergo esophagectomy

and perioperative mortality rates were similar to those previously reported [5, 7, 12, 21].

We found that the pCR rate was 37% in patients who underwent surgical resection and that clinical CR was associated with prolonged PFS ($P = 0.052$) and OS ($P = 0.058$). Higher pCR rates have been observed in patients with squamous cell carcinoma than in those with adenocarcinoma [7, 22]. Squamous cell carcinoma may be more responsive to treatment, and pCR rates in patients with esophageal squamous cell carcinoma are consistently in the range of 25–50% [20]. Despite our previous findings [23], we found no difference in survival outcomes between patients with pCR and residual disease. Although some trials reported that patients who achieved pCR at the time of resection had excellent survival outcomes [24], others did not [25, 26], with 5-year OS rates in patients with and without pCR being 34–62% and 18–41%, respectively [20].

Table 4 Univariate analyses of factors associated with progression-free survival (PFS) and overall survival (OS)

	Factor	*n*	5-year PFS (%)	95% CI	*P* value	5-year OS (%)	95% CI	*P* value
Gender	Male	48	25.9	13.5–38.3	0.073	31.2	18.1–44.3	0.089
	Female	6	55.6	15.8–95.4		66.7	–	
Age (years)	<65	27	37.0	18.8–55.2	0.418	37.0	18.8–55.2	0.727
	≥65	27	23.0	7.1–38.9		37.0	18.7–55.1	
ECOG	PS 0	11	54.5	25.1–83.9	0.042	54.5	25.1–83.9	0.126
	PS 1	43	23.8	11.1–36.5		30.2	16.5–43.9	
Clinical stage	IIA/B	23	29.8	11.1–48.5	0.889	34.8	15.3–54.3	0.960
	III	31	30.4	14.2–46.6		38.7	21.6–55.8	
Tumor location	Upper/middle	24	29.2	11.0–41.4	0.985	37.5	15.1–56.9	0.607
	Lower	30	31.8	15.1–48.5		36.7	19.5–53.9	
Histology	WD/MD	44	30.5	16.9–44.1	0.555	38.6	24.2–53.0	0.695
	PD	10	30.0	1.6–58.4		30.0	16.0–58.4	
Albumin	≤3.9 mg/dl	29	27.2	11.0–43.3	0.714	34.5	17.2–51.8	0.956
	>3.9 mg/dl	25	34.3	15.7–52.9		40.0	20.8–59.2	
Dysphagia	Severe	19	27.4	7.3–47.5	0.576	47.4	24.9–70.0	0.315
	No/mild	35	31.2	15.9–46.5		31.4	16.0–46.8	
Weight loss	Yes	21	25.5	6.9–44.1	0.776	38.1	17.3–58.9	0.689
	No	33	33.1	17.0–49.2		36.4	20.0–52.8	
Clinical response	CR	26	38.1	16.4–56.8	<0.001	46.2	27.0–65.4	0.002
	Improved	26	24.9	8.3–41.5		30.8	13.1–48.5	
	PD	2	0.0	–		0.0	–	
Pathologic CR	Yes	20	38.1	16.8–59.4	0.426	45.0	23.2–66.8	0.971
	Residual	21	28.6	9.3–47.9		38.1	17.3–58.9	
Esophagectomy	Done	41	33.6	19.1–48.1	0.060	41.5	26.4–56.6	0.216
	Not done	13	19.2	0.0–40.6		23.1	0.0–46.0	

ECOG PS Eastern Cooperative Oncology Group Performance Status, *WD* well differentiated, *MD* moderately differentiated, *PD* poorly differentiated, *CR* complete response, *PD* disease progression

Table 5 Multivariate analysis of factors associated with progression-free survival (PFS) and overall survival (OS)

Factor		HR (PFS)	95% CI	*P* value	HR (OS)	95% CI	*P* value
Gender	Male (vs. Female)	4.393	0.987–19.554	0.052	4.547	1.009–20.483	0.049
ECOG	PS 1 (vs. 0)	2.920	1.079–7.897	0.035	2.527	0.925–6.904	0.071
Clinical response	CR	Reference		0.058	Reference		0.052
	Improved	1.280	0.550–2.982		1.229	0.529–2.857	
	PD	8.541	1.441–50.635		9.775	1.526–62.625	
Pathologic response	pCR (+)	Reference		0.813	Reference		0.636
	Residual	0.837	0.324–2.162		0.624	0.236–1.648	
	No esophagectomy	1.101	0.384–3.157		0.730	0.253–2.108	

HR hazard ratio, *ECOG PS* Eastern Cooperative Oncology Group Performance Status, *CR* complete response, *PD* disease progression, *pCR* pathologic complete response

This variability may be attributable to differences in the proportions of patients with various types of tumor histology, differing also in pretreatment stage, clinical characteristics, chemotherapy regimen, and radiation dose. However, the pCR rate we observed was similar to those reported previously [20, 24, 25].

The clinical response to preoperative CCRT has been reported to be prognostic in patients with esophageal squamous cell carcinoma [24]. The addition of induction chemotherapy to preoperative CCRT has been shown to improve tumor response and survival outcomes, via early treatment of micrometastasis, downstaging, and enhancing

the likelihood of complete resection [18, 19]. Moreover, because the response to induction chemotherapy is predictive of patient outcome [27], we added one cycle of induction chemotherapy to CCRT. This allowed treatment to be commenced as early as possible, increased patient compliance by improving subjective symptoms, and enhanced the relative dose intensity of chemotherapy in patients who were intolerant to and discontinued chemotherapy during CCRT. We also found that fewer patients (17%) experienced distant or local recurrence than did those enrolled in previous studies using preoperative CCRT alone (22–28%), supporting the benefits of induction chemotherapy [12, 13]. In addition, such chemotherapy can be used to assess tumor chemosensitivity prior to CCRT, indicating whether the same chemotherapeutic agent(s) should be incorporated into neoadjuvant CCRT. The role of induction chemotherapy is being tested further in our ongoing randomized phase II trial of preoperative concurrent CCRT, with or without two cycles of induction chemotherapy, in patients with resectable esophageal cancer.

Although a meta-analysis showed that trimodal treatment was beneficial [10], the high rate of postoperative mortality and poor patient compliance with surgery are of concern. We observed a 30-day mortality rate of 6%; this may be reduced by utilizing strict criteria for surgery or employing an inter-disciplinary approach. When the present study was initiated, the drop-out rate in representative studies of preoperative CCRT exceeded 25% [9]. Administration of outpatient-based chemotherapy resulted in a lower drop-out rate, 22%, than previously observed when inhospital chemotherapy was employed (31%) [13]. Further work to determine optimal CCRT regimens and schedules is needed not only to improve survival, but also to increase compliance with treatment protocols.

In conclusion, we found that a single cycle of induction chemotherapy, followed by CCRT containing capecitabine and cisplatin and surgery, was well tolerated, yielding favorable outcomes upon long-term follow-up. Thus, this regimen can be regarded as an alternative trimodal approach in patients with resectable esophageal squamous cell carcinoma.

Conflict of Interest None.

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