Patients with ERCC1-Negative Locally Advanced Esophageal Cancers May Benefit from Preoperative Chemoradiotherapy

Min Kyoung Kim,[1,7] Kyung-Ja Cho,[3] Gui Young Kwon,[3] Seung-Il Park,[4] Yong Hee Kim,[4] Jong Hoon Kim,[5] Ho-Young Song,[6] Ji Hoon Shin,[6] Hwoon Yong Jung,[2] Gin Hyug Lee,[2] Kee Don Choi,[2] and Sung-Bae Kim[1]

Abstract

Purpose: To assess the significance of excision repair cross-complementation group 1 (ERCC1) expression as a predictive marker, we analyzed the effects of preoperative chemoradiotherapy on survival relative to ERCC1 status in patients with locally advanced operable esophageal cancer.

Experimental Design: Paraffin-embedded pretreatment tumor specimens, collected by endoscopic biopsy from patients treated with surgery alone or with preoperative chemoradiotherapy followed by surgery, were immunohistochemically assayed for ERCC1 expression.

Results: Of the 175 patients, 152 biopsy specimens were available for immunohistochemical analysis. Based on a median ERCC1 expression score of 1, we divided the samples into ERCC1-positive (score >1; 71 patients, 47%) and ERCC1-negative (score ≤1; 81 patients, 53%) groups. No differences in patient and disease characteristics were observed between the two groups. However, among patients with ERCC1-negative tumors, those who received preoperative chemoradiotherapy had longer overall survival (OS) and event-free survival (EFS) than those treated with esophagectomy alone (median OS, 59.2 versus 25.4 months, $P = 0.057$; median EFS, 50.7 versus 19.7 months, $P = 0.042$). This difference was not observed among patients with ERCC1-positive tumors. In multivariate analysis, treatment modality was the major determinant of both EFS ($P = 0.006$) and OS ($P = 0.008$) for patients with ERCC1-negative tumors, whereas Eastern Cooperative Oncology Group performance status was the only significant predictor of outcome among ERCC1-positive patients. Among patients who received esophagectomy alone, those with ERCC1-positive tumors had a tendency toward longer OS and EFS ($P = 0.085$ and 0.094, respectively).

Conclusions: Patients with ERCC1-negative operable esophageal tumors show a greater benefit from preoperative chemoradiotherapy followed by esophagectomy than those who undergo esophagectomy alone.

Although esophageal cancer is a relatively rare malignancy, it is highly lethal, with a relative 5-year overall survival (OS) rate of under 20% (1). Due to the poor OS rates of patients treated with resection alone, multimodal approaches have been employed; however, randomized trials comparing preoperative combined modality therapy with surgery alone have shown conflicting results (2–6).

In our previous phase III trial, we showed that preoperative chemoradiotherapy induced high clinical and pathologic responses, with a pathologic complete response rate of 43%. However, preoperative chemoradiotherapy did not show a statistically significant benefit on survival compared with surgery alone, and survival analysis including only patients who received the assigned treatment also showed no significant benefit (6). Preoperative chemoradiotherapy may benefit some patients, whereas others may suffer from toxicity or progression of disease without substantial benefit. As a consequence, one of the most relevant issues for patients with resectable esophageal cancer is the need for a reliable method to identify the subgroups of patients most likely to benefit from chemoradiotherapy.

The DNA repair mechanism is one of the crucial molecular pathways potentially involved in resistance to cisplatin-based chemotherapy or chemoradiotherapy. The enzyme excision repair cross-complementation group 1 (ERCC1) plays a rate-limiting role in the nucleotide excision repair pathway, and its expression has been associated with survival in patients with various malignancies (7–9). Previously, we assessed whether expression of ERCC1 can predict outcome after preoperative chemoradiotherapy in patients with localized esophageal cancer (10). Although we found that patients with ERCC1-negative tumors were significantly more likely to achieve pathologic major response, we did not show an obvious survival benefit for

Authors' Affiliations: Divisions of [1]Oncology and [2]Gastroenterology, Departments of Internal Medicine, [3]Pathology, [4]Thoracic and Cardiovascular Surgery, [5]Radiation Oncology, and [6]Diagnostic Radiology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea and [7]Division of Oncology, Department of Internal Medicine, Yeungnam University College of Medicine, Daegu, Korea

Received 11/12/07; revised 3/2/08; accepted 3/20/08.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Requests for reprints: Sung-Bae Kim, Division of Oncology, Department of Internal Medicine, University of Ulsan College of Medicine, Asan Medical Center, 388-1 Poongnap-dong, Songpa-gu, Seoul 138-736, Korea. Phone: 82-2-3010-3217; Fax: 82-2-3010-6961; E-mail: sbkim3@amc.seoul.kr.

doi:10.1158/1078-0432.CCR-07-4848

Table 1. Characteristics of patients

Characteristics	Total (n = 152)	CRT-S group (n = 111)	S group (n = 41)	P	Patients with ERCC1-positive tumors (n = 71)	Patients with ERCC1-negative tumors (n = 81)	P
Age (y)				0.682			0.580
<63	70	50	20		31	39	
≥63	82	61	21		40	42	
Sex				0.071			0.419
Male	136	96	40		62	74	
Female	16	15	1		9	7	
Clinical stage*				0.192			0.655
II	87	60	27		42	45	
III	65	51	14		29	36	
Differentiation of tumors				0.208			0.092
WD	20	11	9		14	6	
MD	101	75	26		44	57	
PD	23	18	5		11	12	
NA	8	7	1		2	6	
Performance status (ECOG)				0.030			0.846
0	15	13	2		6	9	
1	125	86	39		59	66	
2	12	12	0		6	6	
Weight loss				0.237			0.363
<10%	121	90	31		53	68	
≥10%	26	19	7		15	11	
NA	5	2	3		3	2	
Surgery				0.009			0.840
Ivor Lewis	111	79	32		53	58	
Transhiatal	19	19	0		9	10	
McKeown	22	13	9		9	13	
Resection margin				0.293			0.894
R0	148	109	39		69	79	
R1	4	2	2		2	2	
Chemotherapy							0.454
5-Fluorouracil/cisplatin	54	54	NA		35	19	
Capecitabine/cisplatin	57	57	NA		33	24	

Abbreviations: WD, well differentiated; MD, moderately differentiated; PD, poorly differentiated.
*American Joint Committee on Cancer 2002 staging system.

the ERCC1-negative subgroup. To explain the inconsistent effect of ERCC1 expression on response and survival, we hypothesized that ERCC1 may have another biological effect on survival. To assess the significance of ERCC1 expression as a predictive marker, we analyzed the effects of preoperative chemoradiotherapy on survival according to ERCC1 status in patients with locally advanced operable esophageal cancer.

Patients and Methods

Patient selection and evaluation. Beginning in March 1993, we conducted three prospective clinical trials in patients with locally advanced operable esophageal cancer (6, 11, 12). The eligibility criteria for all three trials were identical. From May 1993 to September 2005, 218 patients were treated in the preoperative chemoradiotherapy arm and 50 in the surgery alone arm; of these, 129 patients underwent preoperative chemoradiotherapy and esophagectomy (CRT-S) and 48 underwent esophagectomy (S) alone. For ERCC1 analysis, each case was required to satisfy the following criteria: (*a*) pretreatment pathology available for analysis, (*b*) completion of the assigned treatment, and (*c*) gross complete resection (R0 or R1 resection). Finally, 152 tumor tissues (111 in the CRT-S arm and 41 in the S arm) were available for ERCC1 analysis. The study protocol was approved by the Institutional Review Board for Human Research of Asan Medical Center.

Treatment protocols. Between March 1993 and 1995, neoadjuvant chemotherapy consisted of two cycles of cisplatin (60 mg/m^2 i.v. infusion for 5 h on day 1) and 5-fluorouracil (1,000 mg/m^2/d as a continuous i.v. infusion for 5 days on days 2-6). Beginning in March 1995, the patients were treated with 5-fluorouracil for 4 days (days 2-5), but 5-fluorouracil was omitted during the second cycle of chemotherapy. In group 3, 5-FU was replaced by capecitabine; patients received induction cisplatin (60 mg/m^2 i.v. on day 1) and capecitabine (2,000 mg/m^2/day orally on days 1-14) followed by 1 week of rest. This was followed by cisplatin (30 mg/m^2 i.v. on days 22, 29, 36, and 43) plus capecitabine (1,600 mg/m^2/d orally 5 days/wk), concurrent with radiotherapy. Between March 1993 and 1997, radiotherapy was delivered twice daily, to a dose of 48 Gy, in 40 fractions of 1.2 Gy, with a minimum of 6 h between sessions. Between March 1999 and 2002, 38 fractions of 1.2 Gy each were delivered twice daily for a total dose of 45.6 Gy. After 2003, the fractionation schedule was modified to 46 Gy in 23 fractions within 4 weeks (2 Gy/fraction/d). Surgical resection was done using a transhiatal, abdominal-right thoracic (Ivor Lewis), or right thoracic-abdominal-cervical (McKeown) approach. En bloc lymph node dissection included the periesophageal, infracardial, posterior mediastinal, and paracardial lymph nodes as well as those located along the lesser gastric curvature and at the origin of the left gastric artery, celiac trunk, common hepatic artery, and splenic artery. Resections were considered incomplete when microscopic examination revealed positive margins (R1) or when there was residual gross disease (R2).

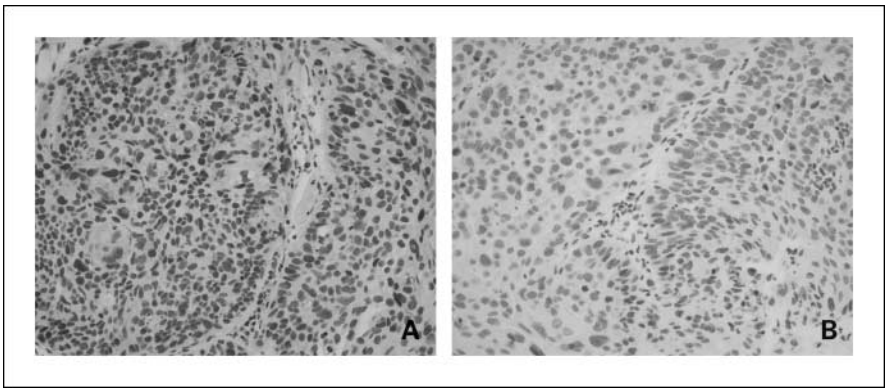

Fig. 1. Immunohistochemical determination of ERCC1 expression (×400). *A,* high expression of ERCC1; strong and diffuse staining (H score 3). *B,* low expression of ERCC1 (H score 0).

Immunohistochemical analysis for ERCC1. Immunostaining was done in a Benchmark automatic immunostaining device (Ventana Medical System) using formalin-fixed, paraffin-embedded tissue blocks. Tissue sections (5 μm thick) on poly-L-lysine-coated slides were exposed to 10 mmol/L citrate buffer (pH 6.0) and heated for 30 min in a water bath for antigen retrieval. Tumor sections were incubated for 60 min with 1:100 dilutions of mouse monoclonal antibodies against human ERCC1 (clone 8F1; Neomarkers). The streptavidin-biotin method, with a peroxidase-containing conjugate, was used for detection, and the peroxidase reaction was developed using diaminobenzidine as the chromogen. The sections were counterstained with Mayer's hematoxylin solution and mounted in a nonaqueous medium. Endothelial cells from tonsils served as external positive controls for ERCC1. As a negative control, the primary antibody was omitted during the staining procedure. Nuclear immunoreactivity caused a sample to be scored as positive for ERCC1. Two independent pathologists (K-J. Cho and G.Y. Kwon) blinded to clinical outcomes analyzed the results. Staining intensities of ERCC1 were graded on a scale of 0 to 3. The percentage of positive tumor nuclei was calculated for each specimen, with 0 indicating 0% staining, 0.1 indicating 1% to 9% staining, 0.5 indicating 10% to 49% staining, and 1 indicating 50% to 100% staining. The proportion score was multiplied by the staining intensity to obtain a semiquantitative H score (0-3; ref. 13). The median value of each score was *a priori* chosen as the cutoff point for separating positive from negative tumors.

Table 2. Patient characteristics according to treatment modality in ERCC1-positive and ERCC1-negative groups

Characteristics	ERCC1 positive			ERCC1 negative		
	CRT-S (*n* = 43)	S (*n* = 28)	*P*	CRT-S (*n* = 68)	S (*n* = 13)	*P*
Age (y)			0.385			0.879
<63	17	14		33	6	
≥63	26	14		35	7	
Sex			0.010			0.894
Male	34	28		62	12	
Female	9	0		6	1	
Clinical stage*			0.114			0.779
II	21	19		39	8	
III	22	9		29	5	
Differentiation of tumors			0.259			0.601
WD	6	8		5	1	
MD	27	17		48	9	
PD	9	2		9	3	
NA	1	1		6	0	
Performance status (ECOG)			0.104			0.188
0	4	2		9	0	
1	33	26		53	13	
2	6	0		6	0	
Weight loss			0.061			0.228
<10%	35	18		55	13	
≥10%	8	7		11	0	
NA	0	3		2	0	
Surgery			0.027			0.134
Ivor Lewis	30	23		49	9	
Transhiatal	9	0		10	0	
McKeown	4	5		9	4	
Resection margin			0.757			0.297
R0	42	27		67	12	
R1	1	1		1	1	
Perioperative mortality	2	0	0.515	4	1	0.804

*American Joint Committee on Cancer 2002 staging system.

Statistical analysis. Categorical variable in two groups was compared by Pearson's χ^2 test or Fisher's exact test, where appropriate. Survival probability analyses were done using the Kaplan-Meier product-limit method. OS was calculated from the date of registration to the date of death from any cause or most recent follow-up. Event-free survival (EFS) was defined as the time from study enrollment to the date of first observation of disease progression, relapse, or death due to any cause. Perioperative mortality was defined as patient death within the first 30 days postoperatively or during the initial hospitalization. Significant between-group differences were assessed by the log-rank test. Multivariate analyses were done using a Cox regression models for EFS and OS. Factors with P values < 0.1 in univariate analyses were examined with multivariate regression models. All statistical tests were two sided, with significance defined as $P < 0.05$. Analyses were done using SPSS version 12.0 (SPSS) and SigmaPlot version 9.0 (Systat Software).

Results

Characteristics of patients. The 152 patients (136 men and 16 women) had a median age of 63 years (range, 39-76 years). Histologically, all primary tumors were squamous cell carcinomas. Ninety-seven percent of tumors originated from the middle and lower esophagus. Patient baseline demographic and clinical characteristics are listed in Table 1. Twelve patients in the CRT-S group had Eastern Cooperative Oncology Group (ECOG) performance status of 2. The method of surgery differed between CRT-S and S- groups, but there were no other significant differences in patient and disease characteristics between CRT-S and S-groups.

Association of biological marker expression with patient and tumor characteristics. Based on a median ERCC1 expression score of 1, we divided the samples into those that were ERCC1 positive (score >1; 71 samples, 46.7%) and ERCC1 negative (score ≤1; 81 samples, 53.3%; Fig. 1). Expression of ERCC1 was not associated with patient and tumor characteristics such as age, sex, tumor differentiation, tumor size, clinical stage, and lymph node metastasis. Table 2 lists patient characteristics according to treatment modality in the ERCC1-positive and ERCC1-negative groups.

Survival according to treatment modality and level of ERCC1 expression. At a median follow-up of 44 months for surviving patients (range, 15.4-152.2 months), median OS was 45.6 months in the S group and 47.8 months in the CRT-S group ($P = 0.763$), and median EFS was 36.7 months in the S group and 38.4 months in the CRT-S group ($P = 0.462$; Table 3; Fig. 2A).

Median OS was 43.2 months in the ERCC1-positive group and 51.2 months in the ERCC1-negative group ($P = 0.735$), and median EFS was 32.6 months in the ERCC1-positive group and 41.6 months in the ERCC1-negative groups ($P = 0.470$; Table 3; Fig. 2B).

Effects of preoperative chemoradiotherapy on survival for patients with ERCC1-negative and ERCC1-positive tumors. Among patients with ERCC1-negative tumors, OS tended to be longer in the CRT-S than in the S group ($P = 0.057$), and the 5-year OS rates among patients with ERCC1-negative tumors were 47.5% in the CRT-S group and 30.7% in the S group (Fig. 2C). EFS was also significantly longer in the CRT-S group than in the S group ($P = 0.042$). Among patients with ERCC1-positive tumors, however, there was no difference in OS ($P = 0.304$) or EFS ($P = 0.516$) between CRT-S and S groups (Fig. 2D), and the 5-year OS rates among patients with ERCC1-positive tumors were 36.7% in the CRT-S group and 42.9% in the S group.

A multivariate analysis evaluated the effect of treatment modality after controlling for clinical stage, performance status, resection margin status, and patient age. Hazard ratio (HR) estimates by ERCC1 status are listed in Table 4. Among patients

Table 3. EFS and OS according to attributed treatment and ERCC1 status

Group	All patients	CRT-S group	S group	*P*
EFS				
Patients with ERCC1-negative tumors				0.042
No. events/total no. patients	43/81	34/68	9/13	
Rate of EFS at 5 y, % (95% CI)	38.6	41.9	25.2	
Median EFS (mo)	41.6	50.7	19.7	
Patients with ERCC1-positive tumors				0.516
No. events/total no. patients	45/71	27/43	18/28	
Rate of EFS at 5 y, % (95% CI)	38.7	26.8	49.7	
Median EFS (mo)	32.6	26.8	43.5	
All patients				0.462
No. events/total no. patients	88/152	61/111	27/41	
Rate of EFS at 5 y, % (95% CI)	39.0	36.2	42.3	
Median EFS (mo)	38.4	38.4	36.7	
OS				
Patients with ERCC1-negative tumors				0.057
No. deaths/total no. patients	39/81	30/68	9/13	
Rate of OS at 5 y, % (95% CI)	44.2	47.5	30.7	
Median OS (mo)	51.2	59.2	25.4	
Patients with ERCC1-positive tumors				0.304
No. deaths/total no. patients	40/71	25/43	15/28	
Rate of OS at 5 y, % (95% CI)	45.1	36.7	42.9	
Median OS (mo)	43.2	39.3	77.7	
All patients				0.763
No. deaths/total no. patients	79/152	55/111	24/41	
Rate of OS at 5 y, % (95% CI)	44.9	43.2	46.3	
Median OS (mo)	47.8	47.8	45.6	

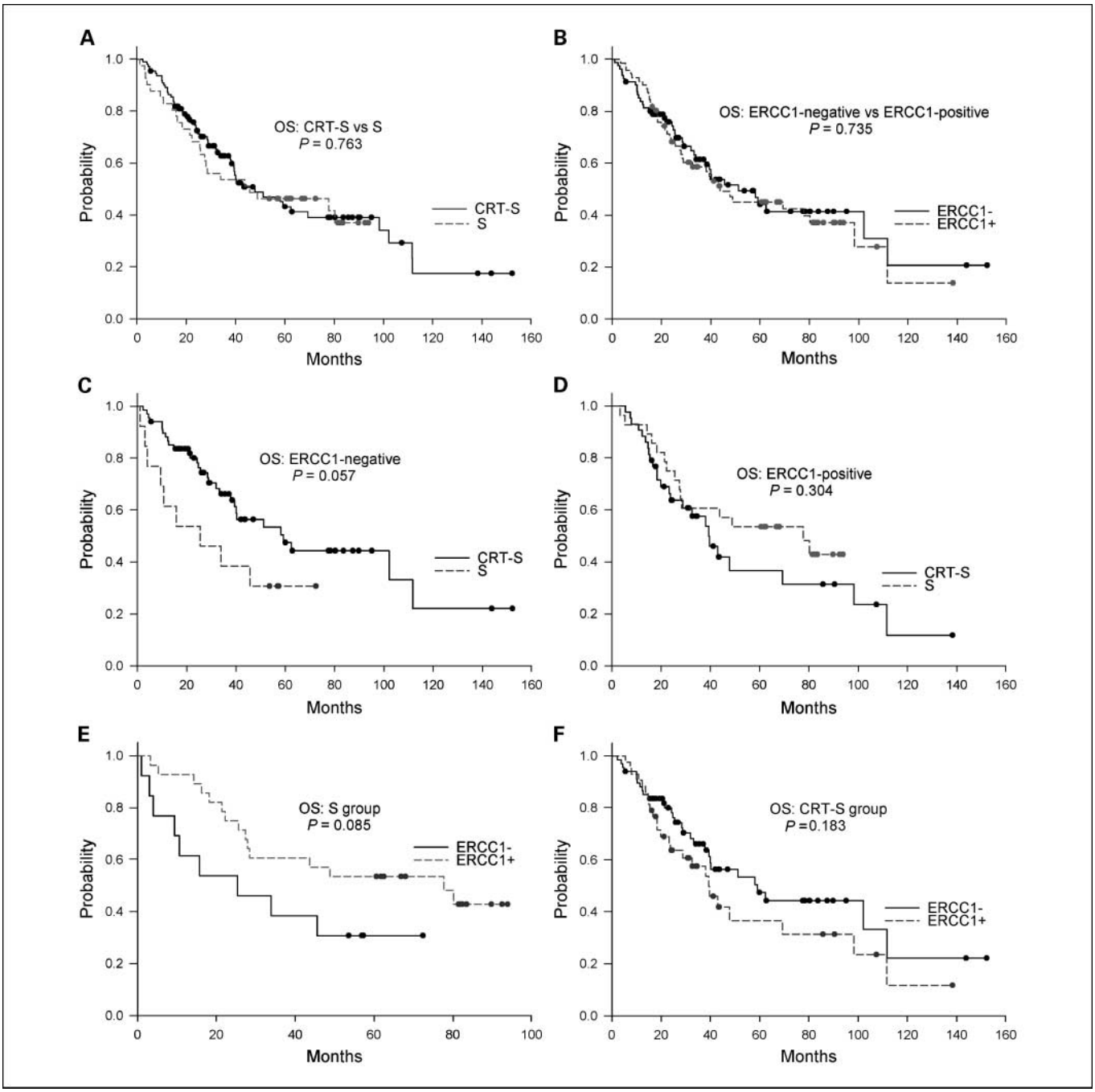

Fig. 2. Kaplan-Meier estimates of the probability of OS. *A* and *B,* OS according to treatment (CRT-S versus S) and ERCC1 expression. *C* and *D,* OS according to treatment (CRT-S versus S) for patients with ERCC1-negative and ERCC1-positive tumors. *E* and *F,* OS according to ERCC1 expression for patients treated with CRT-S or S.

with ERCC1-negative tumors, treatment modality (CRT-S versus S) was an independent prognostic factor for OS [adjusted HR for death, 0.33; 95% confidence interval (95% CI), 0.14-0.75; $P = 0.008$] and for EFS (adjusted HR for death, 0.30; 95% CI, 0.12-0.70; $P = 0.006$). Clinical stage and resection margin status were other independent predictors of survival. Among patients with ERCC1-positive tumors, only ECOG performance status was a significant predictor of outcome for both OS (adjusted HR for death, 0.41; 95% CI, 0.15-1.11; $P = 0.080$) and EFS (adjusted HR for death, 0.31; 95% CI, 0.11-0.89; $P = 0.030$).

Survival according to ERCC1 expression for patients treated with CRT-S or S. Among the S group, which included 28 patients with ERCC1-positive tumors and 13 with ERCC1-negative tumors, the former had a tendency toward longer OS ($P = 0.085$) and EFS ($P = 0.094$; Fig. 2E). In contrast, among the CRT-S group, which included 68 patients with ERCC1-negative tumors and 43 with ERCC1-positive tumors, there are no significant difference in OS between two groups ($P = 0.183$; Fig. 2F). Patients with ERCC1-negative tumors had a tendency toward longer and EFS ($P = 0.094$).

Table 4. HR estimates for treatment modality (CRT-S versus S) by ERCC1 expression adjusting for age, clinical stage, and ECOG performance status

Clinical outcome	ERCC1 negative		ERCC1 positive	
	HR (95% CI)	*P*	HR (95% CI)	*P*
EFS				
Age <63 y	0.90 (0.47-1.74)	0.759	1.57 (0.83-2.97)	0.163
ECOG <1	0.41 (0.15-1.17)	0.095	0.31 (0.11-0.89)	0.030
Stage II	0.35 (0.17-0.74)	0.005	0.65 (0.34-1.24)	0.193
R0 resection	0.15 (0.31-0.70)	0.016	1.47 (0.20-10.89)	0.707
CRT-S arm	0.30 (0.12-0.70)	0.006	1.01 (0.52-1.94)	0.988
OS				
Age <63 y	0.98 (0.49-1.95)	0.955	1.41 (0.71-2.80)	0.321
ECOG <1	0.53 (0.18-1.52)	0.239	0.41 (0.15-1.11)	0.080
Stage II	0.30 (0.14-0.62)	0.001	0.80 (0.40-1.63)	0.544
R0 resection	0.09 (0.02-0.42)	0.002	1.16 (0.15-8.68)	0.887
CRT-S arm	0.33 (0.14-0.75)	0.008	1.17 (0.57-2.43)	0.669

Discussion

We evaluated whether ERCC1 expression could predict the benefit of preoperative chemoradiotherapy in patients with operable esophageal squamous cell cancer. We found that patients with ERCC1-negative tumors may benefit from preoperative chemoradiotherapy when compared with surgery alone.

Platinum has long been the mainstay of chemotherapy for various malignancies, including esophageal cancer. The cytotoxic effect of platinum is attributable to the formation of bulky intrastrand platinum-DNA adducts. Combining cisplatin with radiation has enhanced radiation kill via numerous mechanisms. For example, radiation appears to increase the cellular uptake of platinum drugs and to increase the number of toxic platinum intermediates (14, 15). The level of kill from combined platinum and radiation may also be related to alternations in DNA repair and cell cycle checkpoint functions.

There are at least four main damage repair pathways in mammals: base excision repair, nucleotide excision repair, double-strand break repair, and mismatch repair (16). Nucleotide excision repair is the primary DNA repair mechanism that removes platinum-DNA adducts from genomic DNA and the ERCC1 gene product plays a leading role in the nucleotide excision repair pathway. A relationship between ERCC1 expression and platinum resistance has been observed in patients with gastric, bladder, ovarian, colorectal, and non-small cell lung cancer (7, 8, 17).

Previously, we found that low expression of ERCC1 correlated significantly with good response to preoperative chemoradiotherapy in patients with advanced esophageal cancer (10), suggesting that ERCC1 expression may determine the benefit of preoperative chemoradiotherapy. In the present study, we showed that preoperative chemoradiotherapy may be more effective than immediate surgery in patients with low ERCC1 expression. In contrast, immediate esophagectomy may be as effective as preoperative chemoradiotherapy in patients with high ERCC1 expression. These results are consistent with a prospective study in non-small cell lung cancer, which showed that adjuvant platinum-based chemotherapy, compared with observation, significantly prolonged survival among only patients with ERCC1-negative tumors (13).

Interestingly, our results showed that, after surgery alone, tumors with high ERCC1 expression may have more favorable long-term outcomes than those with low ERCC1 expression. This finding appears to contradict previous reports that tumors with high ERCC1 expression treated with platinum-based chemotherapy have a poor prognosis (7–9). However, it has been suggested that ERCC1 expression has a different prognostic significance in treated and untreated patients (13, 18, 19). We supposed, in agreement with recent hypotheses of DNA repair as a double-edged sword, that the complex biological role of ERCC1 may lead to inconsistent effect of ERCC1 expression on survival (20). The DNA repair capacity is one of the determinants of cancer susceptibility and it is postulated that an intact DNA repair mechanism may reduce the accumulation of genetic aberrations and progression of tumors (20, 21). ERCC1 may not only be responsible for the removal of platinum adducts from DNA but also may be involved in prevention of mutagenesis and progression of cancer.

An individual's genetic constitution is an important regulator of the variability of drug effect. Recent pharmacogenetic studies offer the possibility of tailoring therapy to the specific genetic profile of an individual patient and/or tumor. In the first phase III trial of customized chemotherapy according to ERCC1 mRNA expression in patients with unresectable non-small cell lung cancer, the objective response rate was significantly higher in the genetic arm (50.3%) than in the control arm (39.3%; ref. 22). In this context, our results suggest that individualized chemoradiotherapy according to the level of expression of ERCC1 may have potential benefits in patients with esophageal cancer. However, further validation is necessary to assess the predictive power of the potential marker. On the other hand, single-gene approaches may not reflect the overall complexity of genetic regulation of treatment response. Genomic strategies using global gene expression data may better optimize cancer treatments (23). Gene expression profiling may distinguish among localized esophageal cancers with different pathologic response and survival (24). Further studies are warranted to identify the molecular signatures that can predict outcomes.

The limitations of this study include the inherent weaknesses of immunohistochemical staining, such as its semiquantitative nature, the effects of tissue aging, and interobserver variation. In addition, our study population was quite heterogeneous,

the number of patients was small, and the study was retrospective in design, suggesting that the results should be interpreted cautiously. Prospective studies in larger populations may clarify the effect of ERCC1 expression on survival in patients with operable esophageal cancer.

Despite these limitations, we showed that preoperative chemoradiotherapy had different effects in patients with ERCC1-positive and ERCC1-negative tumors. Our results may help pave the way to providing individualized therapy to patients with operable esophageal cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References

1. Shin HR, Jung KW, Won YJ, Park JG. 2002 Annual report of the Korea Central Cancer Registry: based on registered data from 139 hospitals. Cancer Res Treat 2004;36:103–14.
2. Urba SG, Orringer MB, Turrisi A, Iannettoni M, Forastiere A, Strawderman M. Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal carcinoma. J Clin Oncol 2001;19:305–13.
3. Walsh TN, Noonan N, Hollywood D, Kelly A, Keeling N, Hennessy TP. A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. N Engl J Med 1996;335:462–7.
4. Tepper JE, Krasna M, Niedzwiecki D, et al. Superiority of trimodality therapy to surgery alone in esophageal cancer: results of CALGB 9781 [abstract 4012]. J Clin Oncol 2006;24:18S.
5. Bosset JF, Gignoux M, Triboulet JP, et al. Chemoradiotherapy followed by surgery compared with surgery alone in squamous-cell cancer of the esophagus. N Engl J Med 1997;337:161–7.
6. Lee JL, Park SI, Kim SB, et al. A single institutional phase III trial of preoperative chemotherapy with hyperfractionation radiotherapy plus surgery versus surgery alone for resectable esophageal squamous cell carcinoma. Ann Oncol 2004;15:947–54.
7. Lord RV, Brabender J, Gandara D, et al. Low ERCC1 expression correlates with prolonged survival after cisplatin plus gemcitabine chemotherapy in non-small cell lung cancer. Clin Cancer Res 2002;8:2286–91.
8. Kwon HC, Roh M, Oh S, et al. Prognostic value of expression of ERCC1, thymidylate synthase, and glutathione *S*-transferase P1 for 5-fluorouracil/oxaliplatin chemotherapy in advanced gastric cancer. Ann Oncol 2007;18:504–9.
9. Joshi MB, Shirota Y, Danenberg KD, et al. High gene expression of TS1, GSTP1, and ERCC1 are risk factors for survival in patients treated with trimodality therapy for esophageal cancer. Clin Cancer Res 2005;11:2215–21.
10. Kim MK, Cho KJ, Kwon GY, et al. ERCC1 predicting chemoradiation resistance and poor outcome in oesophageal cancer. Eur J Cancer 2008;44:54–60.
11. Lee JL, Kim SB, Jung HY, et al. Efficacy of neoadjuvant chemoradiotherapy in resectable esophageal squamous cell carcinoma-a single institutional study. Acta Oncol 2003;42:207–17.
12. Kim SB, Park SI, Kim JH, et al. A phase II trial of preoperative one cycle of induction chemotherapy [capecitabine(CAP), CDDP] followed by concurrent chemoradiation (CRT) in patients with resectable esophageal cancer [abstract 4063]. J Clin Oncol 2005;23:16S.
13. Olaussen KA, Dunant A, Fouret P, et al. DNA repair by ERCC1 in non-small-cell lung cancer and cisplatin-based adjuvant chemotherapy. N Engl J Med 2006;355:983–91.
14. Richmond RC. Toxic variability and radiation sensitization by dichlorodiammineplatinum(II) complexes in *Salmonella typhimurium* cells. Radiat Res 1984;99:596–608.
15. Yang LX, Douple EB, Wang HJ. Irradiation enhances cellular uptake of carboplatin. Int J Radiat Oncol Biol Phys 1995;33:641–6.
16. Lindahl T, Wood RD. Quality control by DNA repair. Science 1999;286:1897–905.
17. Bellmunt J, Paz-Ares L, Cuello M, et al. Gene expression of ERCC1 as a novel prognostic marker in advanced bladder cancer patients receiving cisplatin-based chemotherapy. Ann Oncol 2007;18:522–8.
18. Simon GR, Sharma S, Cantor A, Smith P, Bepler G. ERCC1 expression is a predictor of survival in resected patients with non-small cell lung cancer. Chest 2005;127:978–83.
19. Zheng Z, Chen T, Li X, Haura E, Sharma A, Bepler G. DNA synthesis and repair genes RRM1 and ERCC1 in lung cancer. N Engl J Med 2007;356:800–8.
20. Wei Q, Frazier ML, Levin B. DNA repair: a double-edged sword. J Natl Cancer Inst 2000;92:440–1.
21. Spitz MR, Wei Q, Li G, Wu X. Genetic susceptibility to tobacco carcinogenesis. Cancer Invest 1999;17:645–59.
22. Cobo M, Isla D, Massuti B, et al. Customizing cisplatin based on quantitative excision repair cross-complementing 1 mRNA expression: a phase III trial in non-small-cell lung cancer. J Clin Oncol 2007;25:2747–54.
23. Ramaswamy S, Golub TR. DNA microarrays in clinical oncology. J Clin Oncol 2002;20:1932–41.
24. Luthra R, Wu TT, Luthra MG, et al. Gene expression profiling of localized esophageal carcinomas: association with pathologic response to preoperative chemoradiation. J Clin Oncol 2006;24:259–67.

Clinical Cancer Research

Patients with ERCC1-Negative Locally Advanced Esophageal Cancers May Benefit from Preoperative Chemoradiotherapy

Min Kyoung Kim, Kyung-Ja Cho, Gui Young Kwon, et al.

Clin Cancer Res 2008;14:4225-4231.