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Characteristics of Gastric Carcinomas With High ERCC1 Expression and the Prognostic Value of ERCC1 Expression

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Abstract. *Background/Aim: We aimed to evaluate the characteristics of gastric carcinoma with high excision repair cross complementing 1 (ERCC1) expression and the prognostic value of ERCC1 expression. Materials and Methods: ERCC1 expression was evaluated by immunohistochemistry in 309 surgically resected gastric carcinoma specimens using a tissue microarray. Cancer-related survival was analysed using competing risk analysis. Results: Compared to ERCC1-low gastric carcinomas, ERCC1-high gastric carcinomas showed less local invasion (p=0.0013), lower N stage (p=0.0302), earlier pTNM stage (p=0.0003), and less frequent recurrence (p=0002). Patients with ERCC1-high gastric carcinoma showed lower cumulative incidence function estimate of cancer-related death [3.37; 95% confidence intervaI (CI)=0.89-8.75] than did those with ERCC1-low gastric carcinoma (17.12; 95% CI=12.24-22.69; p-value by Gray's test=0.0012). Adjusted proportional sub-distribution hazard ratio for cancer-related death in the patients with ERCC1-high tumour was 0.272 (95% CI=0.084-0.878; p=0.0295). Conclusion: High ERCC1 expression may be an independent positive prognostic marker for gastric carcinoma.*

Since their characterization in 1965, platinum-based agents, including cisplatin [cis-diammineplatinum (II) dichloride], are widely used in the treatment of lung, gastric, urinary bladder, and ovarian cancer (1-4). Cisplatin induces the formation of DNA–DNA intra-strand adducts, which trigger cytotoxic pathways (5). However, the excision repair cross complementing 1 (ERCC1) protein (6, 7) may repair such cisplatin-induced DNA injury in ERCC1-expressing cancer cells, thereby conferring resistance to cisplatin-based chemotherapy. Several studies showed improved treatment outcomes and better prognosis in patients with non-small cell and small cell lung cancer with low ERCC1 expression, compared to those with high ERCC1 expression (8-10). Moreover, high ERCC1 expression was associated with resistance to platinum-based neoadjuvant chemotherapy in advanced gastric carcinoma (AGC) (11-13). However, some studies reported high ERCC1 expression to be associated with better prognosis in patients treated with platinum-based chemotherapy for AGC (14-17).

Higher survival rates in patients with AGC showing high ERCC1 expression may be related to the DNA damage repair mechanisms activated in cancer cells. Although mutations associated with cell proliferation play key roles in the transformation of normal cells into tumour cells (18), the accumulation of many genetic mutations is essential for tumour progression and transformation of tumour cells into metastatic cancer cells (19). ERCC1-mediated repair of DNA injury may interrupt tumour progression and delay cancer cell invasion and metastasis. Therefore, ERCC1-high tumours may be less aggressive and confer better prognosis.

Tumour characteristics and chemotherapy affect prognosis of patients with AGC treated with platinum-based chemotherapy. Therefore, in this study, we investigated the characteristics of ERCC1-high gastric carcinoma and the prognostic value of ERCC1 expression.

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Table I. *Relationship of clinicopathological features with excision repair cross complementing 1 expression.*

		Total (%) (n=309)	ERCC1 expression		*p*-Value
Variable	Subgroup		Low (n=216)	High (n=93)	
Age, year	Median (range)	65 (24-85)	64 (36-85)	60 (24-85)	0.4839
	Female	104 (33.6%)	70 (32.4%)	34 (36.6%)	0.4787
	Male	205 (66.3%)	146 (67.6%)	59 (63.4%)	
Operation, n (%)	Subtotal	219 (70.9%)	147 (68.1%)	7 2(77.4%)	0.1299
	Total	72 (23.3%)	58 (26.8%)	14 (15.1%)	
	Proximal	14 (4.5%)	9 (4.2%)	5 (5.4%)	
	Wedge	4 (1.3%)	2 (0.9%)	2 (2.1%)	
Tumor size, cm	Median (IQR)	3.6 (2.2-5.5)	4.0 (2.0-6.0)	3.0 (1.7-4.5)	**0.0002**
	Range	0.5-17.0	0.5-17.0	0.5-11.0	
Histology, n (%)	WD	65 (21.0%)	39 (18.1%)	26 (28.0%)	0.0588
	MD	99 (32.0%)	65 (30.1%)	34 (36.6%)	
	PD	109 (35.3%)	81 (37.5%)	28 (30.1%)	
	Mucinous	7 (2.3%)	7 (3.2%)	0 (0.0%)	
	SRC	26 (8.4%)	21 (9.7%)	5 (5.4%)	
	Undiff	3 (1.0%)	3 (1.4%)	0 (0.0%)	
Lauren class, n (%)	Intestinal	228 (73.8%)	155 (71.8%)	73 (78.49%)	0.4572
	Diffuse	70 (22.7%)	53 (24.5%)	17 (18.28%)	
	Mixed	11 (3.6%)	8 (3.7%)	3 (3.23%)	
T-Stage, n (%)	T1a	81 (26.2%)	48 (22.2%)	33 (35.5%)	**0.0005**
	T1b	85 (27.5%)	53 (24.5%)	32 (34.4%)	
	T2	36 (11.7%)	25 (11.6%)	11 (11.8%)	
	T3	82 (26.5%)	71 (32.9%)	11 (11.8%)	
	T4	25 (8.1%)	19 (8.8%)	6 (6.5%)	
N-Stage, n (%)	0	209 (67.6%)	135 (62.5%)	74 (79.6%)	**0.0302**
	1	31 (10.0%)	24 (11.1%)	7 (7.5%)	
	2	34 (11.0%)	28 (13.00%)	6 (6.5%)	
	3	35 (11.3%)	29 (13.4%)	6 (6.5%)	
pTMN stage, n (%)	1	186 (60.2%)	114 (52.8%)	72 (77.4%)	**0.0003**
	2	59 (19.1%)	49 (22.7%)	10 (10.8%)	
	3	64 (20.7%)	53 (24.5%)	11 (11.8%)	
Recurrence, n (%)	No	259 (83.8%)	170 (78.7%)	89 (95.7%)	**0.0002**
	Yes	50 (16.2%)	46 (21.3%)	4 (4.3%)	
Chemotherapy, n (%)	No	130 (42.1%)	87 (40.3%)	43 (46.2%)	0.2699
	Platinum-based	155 (50.2%)	109 (50.5%)	46 (49.5%)	
	Other	24 (7.8)	20 (9.3)	4 (4.3)	

SD: Standard deviation; IQR: interquartile range; WD: well-differentiated; MD: moderately differentiated; PD: poorly differentiated; SRC: signet-ring cell carcinoma; undiff: undifferentiated; pTNM: pathological TNM. Bold values indicate statistical significance.

Materials and Methods

Patients. We collected clinicopathological data from electronic medical records of 309 patients with gastric carcinoma treated with gastrectomy at the Gyeongsang National University Hospital, Jinju, Korea, between January 2004 and December 2009. All the tumours were staged using the seventh edition of the American Joint Commission on Cancer (20). The diagnosis was histopathologically confirmed by two experienced pathologists. This study was approved by the Institutional Review Board of Gyeongsang National University Hospital with a waiver of informed consent (2019-03-008).

Tissue microarray (TMA). Core tissue biopsies (2 mm diameter) obtained from individual formalin-fixed paraffin-embedded specimens were arranged in new recipient paraffin blocks. One tissue core from the area near the invasive front (the deepest tumour-host interface) of the gastric carcinoma specimens was analysed.

Immunohistochemistry (IHC) for ERCC1. ERCC1 expression in the 4-μm-thick sections from the TMA blocks was analysed using IHC. The tissue sections were attached to glass slides, deparaffinized, rehydrated, and incubated in 3% hydrogen peroxide for 10 min to block endogenous peroxidase activity. The slides were subsequently heated for 20 min in 10 mmol/l citrate buffer (pH 6.0) in a microwave oven (700 W) and incubated with Ultra V Block (Lab Vision; Thermo Fisher Scientific, Inc., Waltham, MA, USA) for 7 min at room temperature (20-25˚C) to block background staining. The slides were then incubated with monoclonal primary antibody

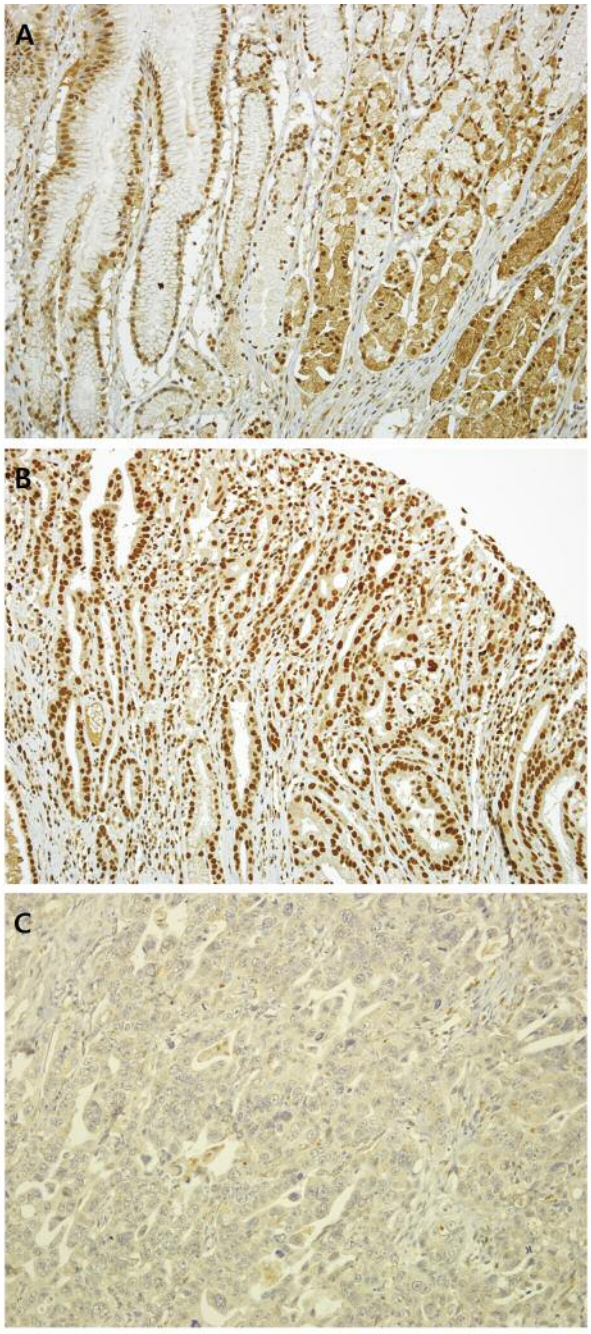

Figure 1. *Immunohistochemical staining for excision repair cross complementing 1 (ERCC1) (×200). A: Normal gastric mucosa. B: High expression of ERCC1 in gastric carcinoma. C: Low expression of ERCC1 in gastric carcinoma.*

to ERCC1 (8F1, 1:100; Abcam, Cambridge, MA, USA) according to the manufacturer's protocols. Ultravision LP Detection System HRP DAB (Thermo Fisher Scientific, Kalamazoo, MI, USA) was used for the visualisation of antigens, and the sections were counterstained using Mayer's haematoxylin.

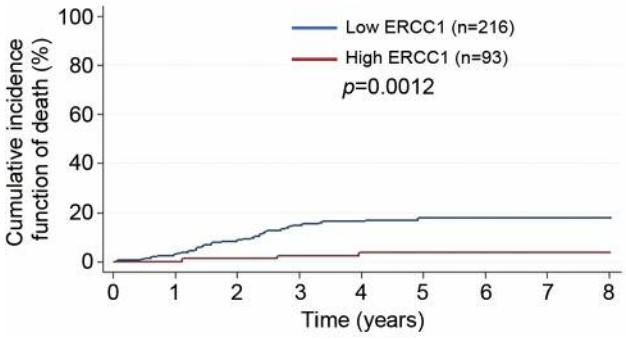

Figure 2. *Cumulative incidence function estimates of death according to excision repair cross complementing 1 (ERCC1) expression.*

Evaluation of IHC. Two pathologists, blinded to the clinical and pathological data of the patients, independently assessed ERCC1 expression and graded the tissues as described previously (14). The ERCC1 expression level was semi-quantitatively scored as low (<10% ERCC1-positive tumour nuclei) and high (≥10% tumour nuclei showing moderate or strong ERCC1 staining).

Statistical analysis. The correlation between ERCC1 expression and clinicopathological variables was evaluated using *t*-test and Pearson's chi-squared test with SAS (ver. 9.4; SAS Institute, Cary, NC, USA). Survival analysis was performed using competing risk analysis and Gray's test. The prognostic value of ERCC1 expression was analysed using the Fine and Gray's sub-hazard model. For all statistical analyses performed, difference with $p<0.05$ were considered significant.

Results

Clinicopathological features of the patients. The clinicopathological features of the patients enrolled in this study are summarized in Table I. Of the 309 patients enrolled, 205 were men and 104 were women, and their median age was 65 years (range=24-85 years). Most patients (186/309; 60.2%) had TNM stage I carcinoma. The recurrence rate was 16.2% (50/310). Approximately half of the patients (155/309; 50.2%) were treated with adjuvant platinum-based chemotherapy and 130 patients (42.0%) did not receive adjuvant therapy.

ERCC1 expression. ERCC1 expression was detected in the nuclei of various cell types. All types of epithelial cells with normal morphology within the gastric specimens showed ERCC1 expression (Figure 1). In addition, most of the fibroblasts and endothelial cells, and a considerable number of inflammatory cells, were ERCC1-positive. Furthermore, ERCC1 expression was observed in tumour cells and varied among specimens.

Clinicopathological features and ERCC1 expression. Compared to ERCC1-low gastric carcinomas, ERCC1-high

Table II. *Competing risk analysis of cancer-related death. Event: Cancer-related death/competing risk event: unrelated death.*

Variable		N	Event (n)	Competing event (n)	CIF at 5 years (95% CI)	*p*-Value*
	Total	304	38	24	12.89 (9.33-17.04)	
Gender	Female	104	12	6	12.32 (6.58-19.96)	0.7329
	Male	200	26	18	13.26 (8.95-18.44)	
Age	≤65 Years	161	24	10	15.33 (10.15-21.50)	0.2119
	>65 Years	143	14	14	9.96 (5.70-15.60)	
Histological type	WD/MD	159	13	14	8.31 (4.65-13.32)	**0.0165**
	Other	145	25	10	17.95 (11.99-24.89)	
Lauren class	Intestinal	223	21	19	9.53 (6.10-13.86)	**0.0061**
	Diffuse/mixed	81	17	5	22.10 (13.44-32.14)	
Tumor size	≤3.7 cm	153	7	10	4.69 (2.07-8.96)	**<0.0001**
	>3.7 cm	151	31	14	21.46 (15.03-28.65)	
T-Stage	1, 2	197	5	11	2.58 (0.97-5.59)	**<0.0001**
	3, 4	107	33	13	32.68 (23.28-42.39)	
N-Stage	0	205	5	12	2.49 (0.94-5.40)	**<0.0001**
	1-3	99	33	12	34.80 (25.09-44.67)	
pTNM stage	I	182	2	10	1.15 (0.23-3.78)	**<0.0001**
	II-IV	122	36	14	30.85 (22.42-39.65)	
Platinum-based chemotherapy	No	254	0	21	9.46 (5.41-14.85)	0.0913
	Yes	50	38	3	16.23 (10.73-22.74)	
ERCC1	Low	212	35	17	17.12 (12.24-22.69)	**0.0012**
	High	92	3	7	3.37 (0.89-8.75)	

CIF: Cumulative incidence function estimates; WD/MD: well-/moderately differentiated; ERCC1: excision repair cross complementing 1. *Gray's test. Bold values indicate statistical significance.

gastric carcinomas had smaller size (p=0.0002), a greater degree of differentiation (p=0.0588), less invasion depth (p=0.0005), lower N stage (p=0.0302), and earlier pathological TNM (pTNM) stage (p=0.0003; Table I). Furthermore, the recurrence rate in patients with ERCC1-high gastric carcinoma was lower than that in patients with ERCC1-low gastric carcinoma (p=0.0002). However, ERCC1 expression did not vary significantly with sex, age, and Laurén classification.

Survival and ERCC1 expression. Survival analysis was performed for 304 patients with survival data, and the 5-year cumulative incidence function estimate of cancer-related death was 12.89 [95% confidence intervaI (CI)=9.33-17.04; Table II]. The cumulative incidence function estimate of cancer-related death for patients with ERCC1-high gastric carcinoma (3.37=95% CI=0.89-8.75) was 5-fold lower than that for patients with ERCC1-low gastric carcinoma (17.12; 95% CI=12.24-22.69; p-value by Gray's test=0.0012; Figure 2). Analysis using Fine and Gray's proportional sub-hazard model revealed an independent positive prognostic value for high ERCC1 expression (adjusted proportional sub-distribution hazard ratio for cancer-related death=0.272, 95% CI=0.084-0.878; p=0.0295).

Discussion

Most of the studies on ERCC1 expression in gastric carcinoma focused on investigating the association between ERCC1 and the response to chemotherapy in a relatively small number of patients with AGC, and the results were controversial (11-17). The main reason for these discrepant results may be the exclusion of patients without chemotherapy, resulting in a lack of comprehensive evaluation of the association between ERCC1 expression and tumour characteristics. In this study, we enrolled a large number of patients with gastric carcinoma, including those with stage I disease and those not treated with chemotherapy, and comprehensively analysed the association between ERCC1 expression and tumour characteristics in gastric carcinoma.

Our results show that high ERCC1 expression in gastric carcinomas is associated with less invasive tumour behaviour and that ERCC1 expression may be an independent positive prognostic marker. In patients with non-small cell lung cancer not treated with adjuvant chemotherapy, those with ERCC1-positive tumours had better prognosis than those with ERCC1-negative tumours (adjusted hazard ratio for death=0.66, 95% CI=0.49-0.90, p=0.009) (8). However, a meta-analysis assessing the predictive value of ERCC1 expression in platinum-based chemotherapy and survival in AGC showed significant associations of high ERCC1 expression with shorter overall survival and lower response to platinum-based chemotherapy in patients receiving palliative chemotherapy (hazard ratio=1.83, 95% CI=1.45-2.31, p<0.001; relative risk=0.49, 95% CI=0.38-0.62, p<0.001) (12). Thus, ERCC1 expression is probably associated with less aggressive tumour

Table III. *Fine and Gray's proportional sub-hazard model analysis. Event: Cancer-related death/competing risk event: unrelated death.*

Variable		Crude model		Adjusted model	
		Proportional sub-distribution HR (95% CI)	*p*-Value*	Proportional sub-distribution HR (95% CI)	*p*-Value*
Gender	Female	1.00			
	Male	1.126 (0.566-2.239)	0.7349		
Age	≤65 Years	1.00			
	>65 Years	0.658 (0.341-1.269)	0.212		
Histological type	WD/MD	1.00		1.00	
	Other	2.225 (1.141-4.339)	**0.0189**	0.841 (0.368-1.925)	0.6826
Lauren class	Intestinal	1.00		1.00	
	Diffuse/mixed	2.409 (1.275-4.552)	**0.0068**	2.034 (0.840-4.924)	0.1157
Tumor size	≤3.7 cm	1.00		1.00	
	>3.7 cm	4.974 (2.190-11.300)	**0.0001**	1.526 (0.605-3.852)	0.3706
T-Stage	1, 2	1.00		1.00	
	3, 4	14.365 (5.541-37.242)	**<0.0001**	1.308 (0.326-5.240)	0.7049
N-Stage	0	1.00		1.00	
	1-3	16.439 (6.398-42.240)	**<0.0001**	3.883 (1.351-11.164)	**0.0118**
pTNM stage	I	1.00		1.00	
	II-IV	31.982 (7.712-132.631)	**<0.0001**	6.741 (0.883-51.451)	0.0658
Platinum-based chemotherapy	No	1.00		1.00	
	Yes	1.751 (0.909-3.373)	0.0938	1.032 (0.536-1.988)	0.9245
ERCC1	Low	1.00		1.00	
	High	0.181 (0.056-0.586)	**0.0043**	0.272 (0.084-0.878)	**0.0295**

WD/MD: Well-/moderately differentiated; ERCC1: excision repair cross complementing 1 (ERCC1). *Gray's test. Bold values indicate statistical significance.

behaviour and poor response to platinum-based chemotherapy. These features of ERCC1 expression in gastric carcinoma may be the reason for the previous contradictory observations for the prognosis of patients with ERCC1-high AGC receiving platinum-based chemotherapy.

Notably, most previous studies showing positive correlation between ERCC1 expression and prognosis in Korean patients with AGC receiving chemotherapy (14, 15, 17). This suggests that *ERCC1* genotype may differ in ethnic groups and may affect the prognosis of patients with gastric carcinoma. In fact, functional single nucleotide polymorphisms of *ERCC1* and *ERCC2* were found to affect the overall survival of Caucasian patients with gastric carcinoma (21). Therefore, Korean patients with gastric carcinoma may have *ERCC1* genotypes associated with better prognosis. Further studies are warranted to determine the *ERCC1* genotype of Korean patients with gastric carcinoma.

The present study has a limitation in that TMA was used to confirm ERCC1 expression. Core tissue biopsies do not represent the complete tumour and cannot account for tumour heterogeneity. However, it was not feasible to perform immunohistochemical staining on each of the 309 tumour sections.

In conclusion, high ERCC1 expression may be an independent positive prognostic marker in gastric carcinoma and may be a possible reason for the controversial observations in the prognosis of patients with high ERCC1-expressing AGC receiving platinum-based chemotherapy.

Conflicts of Interest

The Authors declare no conflicts of interest regarding this study.

Authors' Contributions

Conception and design: Jung Wook Yang, Gyung Hyuck Ko. Development of methodology: Gyung Hyuck Ko. Acquisition of data (clinicopathological data and immunohistochemistry): Jung Wook Yang, Jeong-hee Lee, Jong Sil Lee, Dong Chul Kim, Dae Hyun Song, Se Min Jang, Hyo Jung An, Hyun Min Koh, Minhye Kim, Ji Min Na, Sang-Ho Jeong, Young-Joon Lee, Gyung Hyuck Ko. Analysis and interpretation of data: Jung Wook Yang, Gyung Hyuck Ko. Writing, review/revision of the article: Jung Wook Yang, Gyung Hyuck Ko.

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