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Role of COX2 as a Biomarker for Estimating Survival of Patients With Clinical Stage I Gastric Cancer

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Abstract. *Background/Aim: The prognostic significance of biomarkers related to gastric cancer prognosis has not been fully elucidated. The aim of study was to use immunohistochemical biomarkers to reveal prognosis. Patients and Methods: A total of 682 patients who had undergone curative surgery were evaluated regarding the correlation of prognosis and immunohistochemical biomarkers. Results: The COX2-positive groups showed a poor 5-year overall and disease-free survival. Further analysis revealed that COX2 positivity was a significant risk factor for poorer disease-free survival in the group with clinical stage I disease (p=0.016). We also noted a marked trend between COX2 positivity and poorer overall survival. The COX2-positive group showed general postoperative pathological up-staging compared with the COX2-negative group. Conclusion: This study showed the potential of COX2 as a biomarker for gastric cancer prognosis. Preoperative evaluation of COX2 might be a useful tool for generating optimal treatment strategies in patients with clinical stage I gastric cancer.*

Despite the therapeutic advancements that have been made in recent years, in 2015, gastric cancer was ranked the fifth most common cancer and was third in terms of cancer-related deaths (1). After patients with gastric cancer have received appropriate local treatment (*e.g.* endoscopic submucosal dissection and extended gastrectomy), it is common for the cancer to relapse, thereby necessitating further treatment. In some cases, cancer diagnosis is misjudged and underestimated, resulting in insufficient treatment (2). To overcome this issue, various biomarkers that may help to estimate prognosis regardless of pathological stage have been studied. Some gastric cancer biomarkers, mostly related to cell proliferation and apoptosis, have been identified (3, 4). Since classic clinicopathological features cannot fully predict individual outcomes, it has been argued that molecular biomarkers might potentially be better prognostic traits for gastric cancer.

Studies on the prognostic significance of different molecular markers have included tumor protein 53 (p53), which has been proven to have a significant association with cancer mortality rates (3, 5). Interestingly, Li *et al.* have shown that co-expression of two or more markers, including Ki67, a nuclear protein which is involved in proliferation, has a significant detrimental effect on the survival of patients with gastric cancer (6). Furthermore, cyclo-oxygenase-2 (COX2) has been linked to tumorigenesis, and much of the literature suggests that increased COX2 activity is related to more advanced stages of cancer (7). However, whether COX2 can be used as an independent prognostic factor in gastric cancer is still controversial (8).

The use of biomarkers as a tool for preoperative prognosis prediction and its implications have not yet been fully studied. In current clinical circumstances, immunohistochemistry is the main method used to examine postoperative specimens. In this study, we reinvestigated the potential prognostic use of biomarkers in preoperative settings.

Patients and Methods

Patients. We recruited a total of 738 patients from one institute who underwent gastric cancer surgery between March 2009 to December 2016 all by the same surgeon. Exclusion criteria included all those with clinical stage IV disease according to the seventh edition of the American Joint Committee on Cancer/Union for International Cancer Control classification (9), patients who underwent non-curative resection, and those who had had neoadjuvant chemotherapy. The remaining 682 patients were included in this study, and their specimens were examined by immunohistochemistry. The number of patients with increased expression of p53, COX2, and Ki67 was 665, 661, and 678, respectively. The baseline clinicopathological characteristics were compared between the groups positive and

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Key Words: Stomach neoplasms, immunohistochemistry, cyclooxygenase 2, prognosis.

Table I. *Clinicopathological characteristics for the whole cohort of patients and according t the result of specific immunostaining.*

Variable		Total (n=682)	p53-positive group (n=629)	COX2-positive group (n=623)	Ki67-positive group (n=625)
Gender	Male	433 (63.5%)	398 (63.3%)	396 (63.6%)	394 (63.0%)
	Female	249 (36.5%)	231 (36.7%)	227 (36.4%)	231 (37.0%)
Age, years	Mean±SD	63.8±11.9	60.3±10.2	64.1±12.0	64.0±12.0
Approach, n (%)	Open	77 (11.3%)	73 (11.6%)	74 (11.9%)	75 (12.0%)
	Laparoscopy	589 (86.3%)	540 (85.8%)	528 (84.8%)	535 (85.6%)
	Open conversion	16 (2.3%)	16 (2.5%)	16 (2.6%)	15 (2.4%)
Resection, n (%)	Total gastrectomy	74 (10.8%)	70 (11.1%)	68 (10.9%)	70 (11.2%)
	Completion total	8 (1.2%)	7 (1.1%)	7 (1.1%)	7 (1.1%)
	Distal gastrectomy	551 (80.6%)	512 (81.4%)	508 (81.5%)	508 (81.3%)
	Proximal gastrectomy	42 (6.1%)	34 (5.4%)	34 (5.5%)	34 (5.4%)
	PPG	6 (0.9%)	5 (0.8%)	5 (0.8%)	5 (0.8%)
	Whipple	1 (0.1%)	1 (0.2%)	1 (0.2%)	1 (0.2%)
cStage, n (%)*	I	474 (69.5%)	429 (68.2%)	424 (68.1%)	426 (68.2%)
	II	107 (15.6%)	102 (16.2%)	102 (16.4%)	102 (16.3%)
	III	101 (14.8%)	98 (15.6%)	97 (15.6%)	97 (15.5%)
pStage, n (%)*	Ia	405 (59.4%)	363 (57.7%)	359 (57.6%)	358 (57.3%)
	Ib	67 (9.8%)	64 (10.2%)	66 (10.6%)	65 (10.4%)
	IIa	50 (7.3%)	48 (7.6%)	46 (7.4%)	49 (7.8%)
	IIb	50 (7.3%)	49 (7.8%)	49 (7.9%)	48 (7.7%)
	IIIa	40 (5.8%)	37 (5.9%)	36 (5.8%)	37 (5.9%)
	IIIb	40 (5.8%)	39 (6.2%)	39 (6.3%)	38 (6.1%)
	IIIc	29 (4.2%)	28 (4.5%)	28 (4.5%)	29 (4.6%)
	IV	1 (0.1%)	0 (0%)	0 (0%)	0 (0%)

COX2: Cyclo-oxygenase 2; cStage: clinical stage; pStage: pathological stage; PPG: pylorus-preserving gastrectomy. *Seventh edition (9).

negative for each biomarker, and analysis of overall (OS) and disease-free (DFS) survival was performed. Biomarkers that led to significant differences in survival rates underwent further analysis depending on the preoperative clinical stage. Comparative analysis for clinicopathological characteristics was also carried out among the same clinical staging groups. This study was approved by the institutional review board (IRB number: SC18RESI0030).

Immunohistochemical scoring. Immunostaining for p53, COX2, and Ki67 proteins was performed on formalin-fixed paraffin-embedded tissue, using Ventana automated immunostainer BenchMark Ultra (Ventana Medical Systems, Tucson, AZ, USA) and an UltraView™ Universal DAB Detection Kit (Ventana Medical Systems) according to the manufacturer's instruction. Briefly, slides were dried at 60˚C for 1 h and deparaffinized using EZ Prep (Ventana Medical Systems) at 75˚C for 8 min. Cell conditioning was performed using CC1 solution (Ventana Medical Systems) at 100˚C for 48 min. The representative paraffin sections with a thickness of 4 mm was immunostained with primary antibodies against COX2 (prediluted, rabbit monoclonal; Cell Marque, Darmstadt, Germany), Ki67 (prediluted, rabbit monoclonal; Ventana Medical Systems), and p53 (prediluted, rabbit monoclonal; Ventana Medical Systems). Palatine tonsils and normal liver tissue for p53 and Ki67, and colonic adenocarcinoma tissue for COX2 served as positive controls. Immunohistochemical staining was interpreted as positive when nuclear staining for p53 or Ki67 and cytoplasmic staining for COX2 were evident. The degree of immunoreactivity for each protein was evaluated at the invasive front of the tumor and was scored semi-quantitatively on the basis of the proportion of positive cells. For p53 and COX2, positive samples were defined as those having over 10% positively stained cells.

Statistical analyses. Comparisons between groups were evaluated with Student's *t*-test in continuous variables and chi-squared and Fisher's exact test in nominal variables. Multivariate analysis to determine independent risk factors for postoperative complications underwent binary logistic regression analysis. Statistical significance was inferred when $p<0.05$. The Kaplan-Meier method was used to analyze the overall and disease-free survival. Survival analysis was performed globally and at each clinical stage for each immunohistochemical group. All of the analysis was performed using the software package, PASW 18.0 for Windows (SPSS, Inc., Chicago, IL, USA).

Results

A total 682 patients was included in this study, and tumor stage was distributed like followings according to 7th AJCC/UICC: 405 (59.4%) IA, 67 (9.8%) IB, 50 (7.3%) IIA, 50 (7.3%) IIB, 40 (5.8%) IIIA, 40 (5.8%) IIIB, 29 (4.2%) IIIC, and 1 (0.1%) stage IV. We found that 10% of patients underwent total gastrectomy, whereas 80% underwent distal gastrectomy (Table I). As a whole, the numbers of patients with increased expression of p53, COX2, and Ki67 were 665, 661, and 678, respectively. Ki67 grading was considered positive according to cut-off values of 30%, 40%, and 50%.

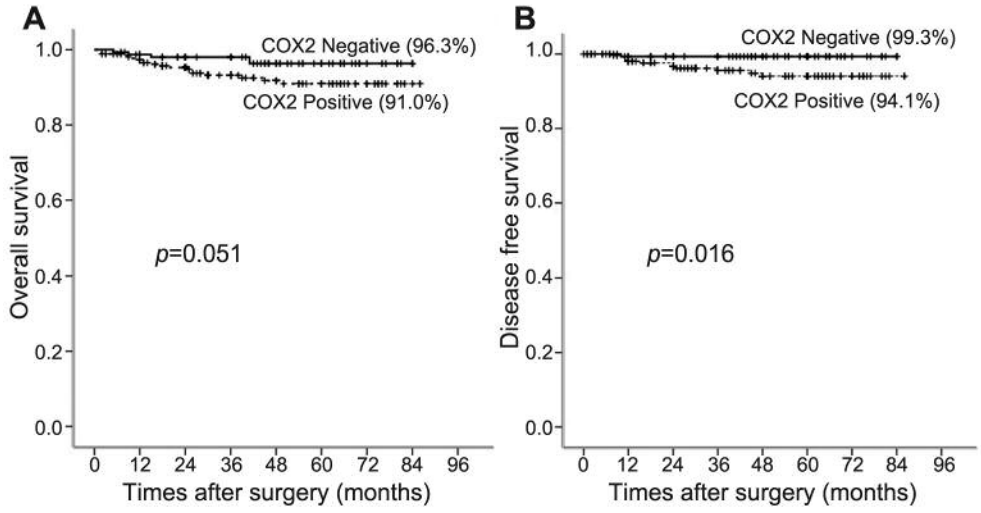

Figure 1. *Survival of patients with clinical stage I gastric cancer according to cyclo-oxygenase 2 (COX2) status. The 5-year rates are shown in parentheses.*

Table II. *Five-year overall (OS) and disease-free (DFS) survival for each immunohistochemical group.*

Variable	Positive group			Negative group			*p*-Value	
	N	OS (%)	DFS (%)	N	OS (%)	DFS (%)	OS	DFS
p53	293	82.0	86.8	335	86.5	89.7	0.142	0.283
COX2	405	82.4	86.6	217	89.2	91.8	0.018	0.040
Ki67_30%	520	82.3	87.0	155	89.9	90.4	0.040	0.276
Ki67_40%	467	82.5	86.8	208	87.9	89.9	0.072	0.333
Ki67_50%	408	82.8	87.0	267	87.6	89.6	0.110	0.440

COX2: Cyclo-oxygenase 2; Ki67_#%: percentage cutoff for Ki67 positivity.

Survival analysis showed that 5-year OS for the COX2- and Ki67-30%-positive groups was poor compared to the negative groups (positive *vs*. negative: COX2: 82.4% *vs*. 89.2%, p=0.018; Ki67: 89.9% *vs*. 82.3%, p=0.040). We also found that the COX2-positive group had worse 5-year DFS (positive *vs*. negative=86.6% *vs*. 91.8%, p=0.040) (Table II). For the rest of the groups, we did not find any significant differences in OS and DFS between the positive and negative groups.

Results from the survival analysis according to clinical stage showed that the main differences were observed in patients with clinical stage I. Results from the COX2 subgroup analysis indicated COX2 positivity to be a significant risk factor for poorer DFS (5-year survival COX2 positive *vs*. negative=94.1% *vs*. 99.3%, p=0.016). OS was also significantly reduced in patients with clinical stage I COX2-positive disease (Figure 1) (Table III).

Comparative analysis between patients with clinical stage I COX2-positive and -negative disease also demonstrated significant differences in pathological staging. Tumor size was larger in the COX2-positive group (2.8±1.9 *vs*. 2.4±1.5 cm). In terms of pathological depth, more T3 and T4a cases were observed in the COX2-positive group compared to the COX2-negative group [20 (7.4%) *vs*. 3 (1.9%), respectively, p=0.015]. For TNM staging, the COX2-positive group included more patients with stage III disease compared to the negative group [8 (3.0%) *vs*. 0 (0%), respectively, p=0.029] (Table IV). Moreover, the COX2-positive group tended to show pathological up-staging postoperatively. In short, there would be a possibility of stage migration compare to preoperative clinical stage. For the COX2-positive group, postoperative stage migrated even to stage IIIb, whereas the highest pathological stage migration was IIb in negative group.

Discussion

Despite ongoing efforts to identify factors which can be used to predict prognosis in patients with gastric cancer, the survival rates for these patients has not improved.

Table III. *Five-year overall (OS) and disease-free (DFS) survival for cyclo-oxygenase 2 (COX2)-positive and -negative groups according to clinical stage.*

Clinical stage		COX2-Positive		COX2-Negative		*p*-Value
		N	Survival (%)	N	Survival (%)	
I	OS	268	91.0	156	96.3	0.051
	DFS	268	94.1	156	99.3	0.016
II	OS	69	78.9	33	72.9	0.930
	DFS	69	84.4	33	78.1	0.513
III	OS	68	49.2	28	65.1	0.145
	DFS	68	56.1	28	61.1	0.208

Clinicopathological factors that are related to prognosis include depth of tumor invasion, histological type, and clinical stage (2, 6). Owing to the fact that a major part of the cellular signaling pathways of cancer pathogenesis has not yet been thoroughly identified, molecular biomarkers that can affect individual outcomes are of great interest.

Traditionally, various cell-cycle-related molecular biomarkers were believed to be promising prognostic factors for gastric cancer survival. However, more recent research has shown that molecular biomarkers that are related to the growth or apoptosis of cancer cells may be useful for predicting the prognosis of patients with cancer (10). These biomarkers include p53, Ki67, human epidermal growth factor 2 (erb-b2 receptor tyrosine kinase 2, HER2/ERBB2), epidermal growth factor (EGFR), and COX2 (3, 6). Additional studies have also implicated cell-cycle regulators including cyclin E, p53 and p27 as potential biomarkers. Recently, there has also been increased interest in the role of cell-adhesion molecules (*e.g.* E-cadherin, CD44, matrix metallopeptidase1) in cancer (11-13).

Loss of function mutations in *p53* have been shown to correlate with poor survival in cancer (3, 5). HER2, is known to up-regulate downstream proliferation signaling pathways and was once believed to be an important independent prognostic indicator. However, a systematic review in 2013 concluded that HER2 could be used to estimate the prognosis of patients with gastric cancer (14). Co-expression of Ki67, a biomarker for cell proliferation, with octamer-binding transcription factor 4 and proliferating cell nuclear antigen has been shown to negatively affect survival (6).

COX2 has been shown to be implicated in tumorigenesis in animal models (15). COX2 is also involved in the up-regulation of angiogenesis due to increased vascular endothelial growth factors and prostaglandin E_2 (16, 17). There is also evidence suggesting that increased COX2 activity is related to more advanced tumor stage (7) but the prognostic role of COX2 in gastric cancer is still controversial. A meta-analysis study from 2014 concluded that elevated COX2 expression can be an independent risk factor for poor OS of patients with gastric cancer but no significant relationship was identified between COX2 overexpression and DFS (8).

The COX2 signaling pathway is responsible for the production of prostaglandins and other cytokines. As a result, significant efforts have been made to discover the association between COX2 and different hallmarks of cancer. In our study, the COX2 and Ki67-30% positive groups showed significant differences in the 5-year OS, and the COX2-positive group also showed advanced pathological staging. We found that 66% of patients with clinical stage I gastric cancer and 34% of those with advanced gastric cancer (higher than stage I) were in the COX2-positive group. Moreover, patients with clinical stage I who were in the COX2-negative group showed better DFS. These results clearly illustrate the prognostic significance of COX2 in clinical stage I gastric cancer. Our findings are backed up by strong data that suggest that there is an association between cancer progression, aggressiveness, lymph nodal metastasis, and COX2 expression (18).

Traditionally, specific clinicopathological features are known to influence the survival of patients with gastric cancer. These include T and N staging, histological type, resection type, and the extent of lymphadenectomy (2, 19). Occasionally cases of very advanced gastric cancer, which were considered to be early-stage cancer in the preoperative setting, are diagnosed during surgery (2). Consequently, preoperative underdiagnosis can negatively alter the prognosis and the postoperative treatment plan of patients.

In current clinical practices, postoperative pathology has proven to be the most reliable method of predicting prognosis in gastric cancer. However, pathological diagnosis is based on full specimen analysis, which only can be achieved following surgery. Under these circumstances, the importance of a comprehensive diagnostic approach and a prediction of preoperative evaluation cannot be emphasized enough.

Despite not being statistically significant, the COX2-positive group tended to show increased pathological up-staging compared to the preoperative clinical staging in our study. Further investigation into COX2 positivity and its relationship with the clinical underdiagnosis of patients who showed unexpected outcomes after curative surgery would be informative.

As mentioned above, the current study represents an opportunity for the use of preoperatively evaluated molecular biomarkers as a tool to make more informed surgical decisions. In clinically obscure cases in which advanced stage is suspected, additional examination of biomarkers might change treatment plans, including the approach or extensiveness of the surgery.

Our study reveals the necessity for additional gene-based prognostic biomarkers. Since current trends in cancer biology have moved towards personalized medicine, a tailored operative approach based on standardized curative surgery is an important emerging topic. Molecular biomarkers which are

Table IV. *Pathological data of patients with clinical stage I gastric cancer according to cyclo-oxygenase 2 (COX2) status.*

Variable		COX2		*p*-Value
		Negative	Positive	
Gender, n (%)	Male	99 (63.5%)	163 (60.8%)	0.606
	Female	57 (36.5%)	105 (39.2%)	
Age, years	Mean±SD	61.9±12.1	63.8±12.3	0.121
BMI, kg/m^2	Mean±SD	23.9±4.0	23.7±3.4	0.492
Approach, n (%)	Open	10 (6.4%)	16 (6.0%)	0.550
	Laparoscopy	146 (93.6%)	250 (93.3%)	
	Open conversion	0 (0.0%)	2 (0.7%)	
Resection, n (%)	Total gastrectomy	6 (3.8%)	15 (5.6%)	0.383
	Distal gastrectomy	135 (86.5%)	236 (88.1%)	
	Proximal gastrectomy	12 (7.7%)	12 (4.5%)	
	PPG	1 (0.6%)	4 (1.5%)	
	Completion total	2 (1.3%)	1 (0.4%)	
LN dissection, n (%)	D1+	114 (73.0%)	198 (73.9%)	0.856
	D2	42 (26.9%)	70 (26.1%)	
Tumor size, cm	Mean±SD	2.4±1.5	2.8±1.9	0.031
Retrieved LNs	Mean±SD	34.5±14.2	33.5±14.1	0.482
T-Stage, n (%)	Tis	1 (0.6%)	0 (0.0%)	0.077
	T1	137 (87.8%)	225 (84.0%)	
	T2	15 (9.6%)	23 (8.6%)	
	T3	3 (1.9%)	17 (6.3%)	
	T4a	0 (0.0%)	3 (1.1%)	
N-Stage, n (%)	N0	142 (91.0%)	232 (86.6%)	0.526
	N1	7 (4.5%)	20 (7.5%)	
	N2	6 (3.8%)	9 (3.4%)	
	N3a	1 (0.6%)	5 (1.9%)	
	N3b	0 (0.0%)	2 (0.7%)	
Stage, n (%)*	Ia	131 (84.0%)	204 (76.1%)	0.293
	Ib	13 (8.3%)	30 (11.2%)	
	IIa	7 (4.5%)	17 (6.3%)	
	IIb	5 (3.2%)	9 (3.4%)	
	IIIa	0 (0.0%)	5 (1.9%)	
	IIIb	0 (0.0%)	3 (1.1%)	
Depth, n (%)	EGC	138 (88.5%)	225 (84.0%)	0.202
	AGC	18 (11.5%)	43 (16.0%)	
Differentiation, n (%)	Differentiated	75 (48.1%)	145 (54.1%)	0.231
	Undifferentiated	81 (51.9%)	123 (45.9%)	
Vascular invasion, n (%)	Negative	154 (98.7%)	264 (98.5%)	>0.99
	Positive	2 (1.3%)	4 (1.5%)	
Lymphatic invasion, n (%)	Negative	136 (87.2%)	221 (82.5%)	0.216
	Positive	20 (12.8%)	47 (17.5%)	
Perineural invasion, n (%)	Negative	148 (94.9%)	248 (92.5%)	0.421
	Positive	8 (5.1%)	20 (7.5%)	
Tumor Infiltration, n (%)	Expansile	42 (27.1%)	59 (22.0%)	0.405
	Intermediate	52 (33.5%)	104 (38.8%)	
	Infiltrative	61 (39.4%)	105 (39.2%)	
Lauren type, n (%)	Intestinal	81 (51.9%)	135 (50.4%)	0.976
	Diffuse	47 (30.1%)	84 (31.3%)	
	Mixed	28 (17.9%)	48 (17.9%)	
Hospital stay, days	Mean±SD	8.7±3.6	9.3±5.0	0.221
Complication, n (%)	No	120 (76.9%)	202 (75.4%)	0.726
	Yes	36 (23.1%)	66 (24.6%)	

AGC: Advanced gastric cancer; EGC: early gastric cancer; LNs: lymph nodes. *Seventh edition (9).

often evaluated by immunohistochemistry during preoperative workup in South Korea, might therefore be useful prognostic markers for estimating patient survival.

It is important to note that there are a few limitations to this study. As the COX2-positive group showed a higher stage migration compared to the negative group, additional factors which alter preoperative staging should also be evaluated in detail, especially because tumor- and patient-related factors can affect clinical staging. Furthermore, the question of whether co-expression of other markers related to the COX2 signaling pathway can affect mortality should also be answered in future studies.

Unfortunately, the specific HER2 status of patients was not included in this study. Data from the Trastuzumab for Gastric Cancer (ToGA) trial has shown that trastuzumab combination therapy improves mortality rates for advanced HER2-positive gastric cancer (20). In the ToGA trial, HER2 scoring was determined by immunohistochemical protein expression and fluorescence *in situ* hybridization (FISH), which is widely accepted as a standard method of HER2 diagnosis. FISH is limited for cases with equivocal (IHC2+) HER2 expression. At the time of this study, most equivocal (IHC2+) cases had not undergone FISH testing because of cost barriers.

As this was a retrospective cohort study at a single center, only a small number of patients were enrolled. Additional multicenter-based trials with similar settings are required to achieve better results. Newly identified biomarkers, including E-cadherin, mutL homolog 1 and CpG island methylator phenotype, are currently under consideration as possible novel prognostic factors. At the time of this study, the aforementioned biomarkers were not evaluated at our center. Therefore, additional analyses of these new biomarkers should be performed in future studies.

Conclusion

This study illustrates the potential of COX2 as a novel biomarker for gastric cancer prognosis. Preoperative evaluation of COX2 might be a useful tool for developing optimal treatment strategies for gastric cancer, specifically for patients with clinical stage I.

Conflicts of Interest

All Authors have no conflicts of interest to disclose.

Authors' Contributions

This study was designed and directed by Dong Jin Kim and Wook Kim. Data were collected and analyzed by Dong Jin Kim. Tae Jung Kim performed and analyzed the immunohistochemistry results on specific biomarkers. The article was written by Dong Jin Kim and Hyun Joo Yoo and commented on by all Authors.

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