Jpn J Clin Oncol 2009;39(5)290–296
doi:10.1093/jjco/hyp020

Expression of the Antiapoptosis Gene *Survivin* Predicts Poor Prognosis of Stage III Gastric Adenocarcinoma

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Received December 12, 2008; accepted February 20, 2009; published online March 31, 2009

Objective: This study was designed to determine the level of survivin expression and its clinical significance as a prognostic factor in Stage III gastric adenocarcinoma.
Methods: We performed immunohistochemical staining for survivin, p53 and Bax in formalin-fixed, paraffin-embedded blocks from 157 surgically resected Stage III gastric cancer tissues. To determine the association with clinical course, we reviewed the patients' clinical records.
Results: Of the 157 gastric cancer tissues, 63 (40.1%) cases showed positive expression for survivin protein. There was no significant association between survivin expression and p53 or Bax. For clinicopathologic parameters, large tumor size was closely related to survivin expression ($P < 0.05$). The 5-year survival rate of patients with positive survivin expression was significantly lower compared with that for survivin-negative cancer patients ($P < 0.05$). Survivin and p53 were independent prognostic factors in Stage III gastric cancer.
Conclusions: Survivin protein is an important predictive and prognostic parameter of poor outcome in gastric carcinoma.

Key words: survivin – antiapoptosis – inhibitors of apoptosis proteins – prognosis – Stage III gastric cancer

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INTRODUCTION

Despite its declining incidence, gastric cancer is still one of the most common malignant tumors worldwide. In the last few decades, patient survival has improved as a result of early detection, development of surgical technique and use of more effective anticancer agent (1). However, despite aggressive treatment, prognosis of patients with advanced gastric cancer remains poor (2). It is linked not only to the high disease stage, but also to the biologic aggressiveness of individual disease, which is characterized by high potential for metastasis and resistance to anticancer therapy (3). To identify the risk factors for poor prognosis and adopt more aggressive treatment, researchers have studied many molecular markers that are associated with prognosis of gastric carcinoma (4).

Aberrations of programmed cell death (apoptosis), which are thought to preserve normal homeostasis and organ morphogenesis, play a role in various human diseases (5). The inhibitors of apoptosis proteins (IAPs) comprise a family of highly conserved cell death inhibitors that have been found in yeast, invertebrates and vertebrates (6). Survivin is a recently discovered IAP that regulates cell division and suppresses apoptosis. It inhibits apoptosis by binding specifically to the terminal-effected cell death proteases, caspase-3 and caspase-7, *in vitro*, thereby inhibiting caspase activity and apoptosis in cells exposed to diverse apoptotic stimuli (7). Survivin is undetectable in most normal adult tissues; however, it is abundantly expressed in fetal tissues including lung, liver, heart and gastrointestinal tract and is also overexpressed in a variety of human neoplasms, suggesting that reactivation of the survivin gene frequently occurs in cancer (8). In some reports, high survivin expression by cancers is correlated with more aggressive behavior in several neoplasms (9). As a prognostic factor, survivin expression is significantly associated with poor clinical outcome in cancers, such as liver (10), colorectal (11), breast (12), lung (13) and esophageal cancer (14).

Survivin expression in gastric carcinoma has been studied, but various rates of expression are reported in earlier studies.

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In addition, the impact on clinicopathologic characteristics and prognosis is largely unknown (15,16). In the present study, we investigated survivin expression levels in tissue from Stage III gastric cancer patients by using tissue microarray and immunohistochemical technologies and determined the association between survivin expression and clinical outcome.

PATIENTS AND METHODS

Patients and Specimens

We studied a series of 157 patients with pathologically proven Stage III gastric adenocarcinoma who did not receive any form of treatment prior to surgery. The surgically resected specimens used for this study were obtained from patients with gastric carcinoma who underwent potentially curative resection (R0) at our hospital during the period from 1989 to 2001. The patients comprised 102 males and 55 females, and the mean age was 57.8 years (Table 1). Clinicopathologic parameters were assigned according to the principles outlined by the Japanese Classification of Gastric Carcinoma (17). Formalin-fixed, paraffin-embedded blocks from surgically resected gastric cancer tissues were studied.

Table 1. Clinicopathologic characteristics of 157 patients with Stage III gastric cancer

Variables	Values (%)
Age (years, mean ± SD)	57 ± 11
Gender	
Male	102
Female	55
Tumor size (cm)	6.4 ± 2.8
Tumor location	
Upper	14
Middle	54
Lower	88
Whole	1
Type of resection	
Total gastrectomy	49
Subtotal gastrectomy	108
Differentiation	
Differentiated	67
Undifferentiated	90
Depth of tumor invasion	
pT2	49
pT3	105
pT4	3
Lymph node metastasis	
pN0	3
pN1	55
pN2	99
Lymphatic invasion	
Negative	12
Positive	145
Vascular invasion	
Negative	137
Positive	20
Perineural invasion	
Negative	50
Positive	107
Lauren classification	
Intestinal	51
Diffuse	70
Mixed	36

Tissue Microarray

To construct the tissue microarray block, two pathologists screened the histologic sections and selected areas representative of the tumor cells. Two and one tissue core samples from each cancer and normal area were taken and placed in a new recipient paraffin block using a commercially available microarray instrument (Micro Digital Co., Korea). After construction, 5 μm sections were cut and hematoxylin and eosin staining was performed on the initial slide to verify the histology.

Immunohistochemical Staining of Survivin, p53 and Bax

Immunohistochemical staining was performed on 5 μm sections of the tissue microarray blocks using a Lab Vision Autostainer LV-1 (LabVision/Neomarkers, Fremont, CA, USA) according to the manufacturer's protocol. Paraffin sections were mounted on superfrost glass slides, deparaffinized and rehydrated in a graded ethanol series. The antigen was retrieved with 0.01 M citrate buffer (pH 6.0) by heating the sample in a microwave vacuum histoprocessor (RHS-1, Milestone, Bergamo, Italy) at a controlled final temperature of 121°C for 15 min. Endogenous peroxidase activity was blocked by incubating the slides in 3% hydrogen peroxide in methanol for 10 min. The primary antibodies were diluted in Dako Antibody Diluent (Dako, Carpentaria, CA, USA) with background-reducing components and were used at the following dilutions: survivin (1:1000, polyclonal, Novus, Littleton, CO, USA), p53 (1:100, clone DO-7, monoclonal, Dako) and Bax (1:50, clone 2D2, Thermo Scientific, Fremont, CA, USA). The primary antibodies were incubated at room temperature for 30 min and detected using the Envision Plus System (Dako). The immunoreaction was

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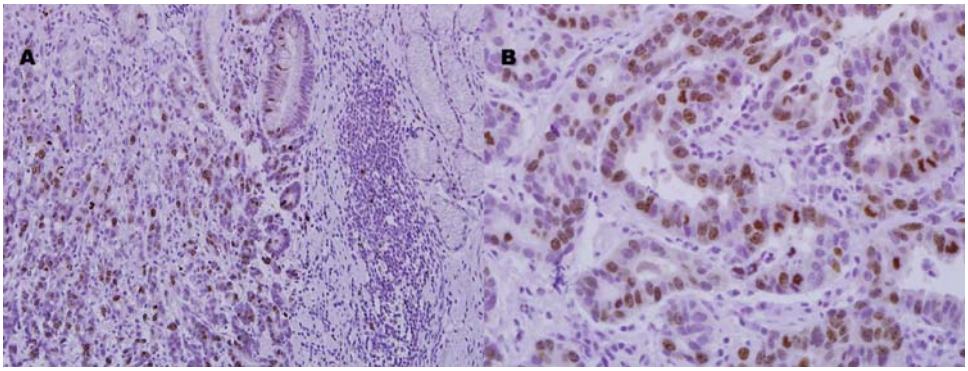

Figure 1. Immunohistochemical staining for survivin. Survivin expression was restricted to the nuclei of tumor cells within the glandular structure. The neighboring normal mucosal epithelium showed focal nuclear expression of survivin only in the neck region and in chronic inflammatory cells (A, ×200; B, ×400).

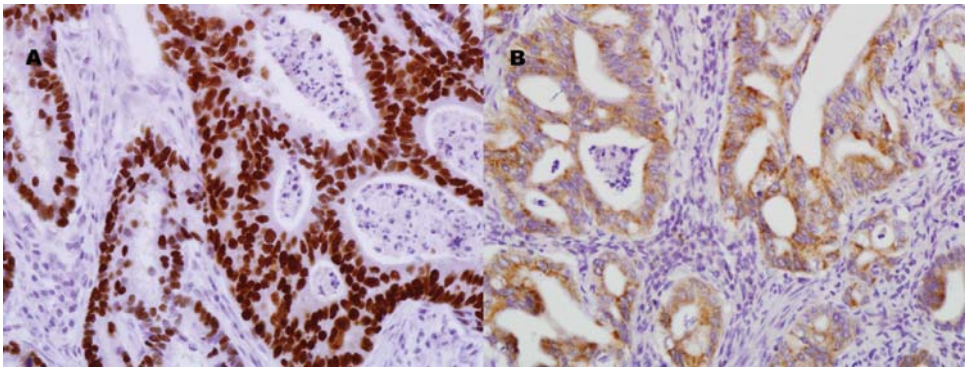

Figure 2. Immunohistochemical staining for p53 and Bax (×400) (A, p53; B, Bax). Normal gastric mucosa showed focal and weak p53 and Bax expression, whereas gastric cancer cells showed moderate to strong p53 and Bax protein expression in nucleus and cytoplasm of the cancer cells, respectively.

developed with diaminobenzidine (DAB, Dako) for 5 min and counterstained with hematoxylin.

Results were interpreted by one pathologist (C.K.J.), who was blinded to the specific diagnosis and prognosis for each case. Staining intensities were scored as negative (0), weakly positive (1+) or strongly positive (2+). Immunostaining results were considered to be positive when ≥10% of the cancer cells showed distinct immunoreactivity.

Statistical Analysis

Variables associated with survivin expression as well as the correlation between survivin and p53 or Bax expression were analyzed by χ^2 test. The survival curves were plotted according to the Kaplan–Meier method and checked by log-rank test. A value of $P < 0.05$ was considered statistically significant.

RESULTS

Expression of Survivin, p53 and Bax

Survivin was exclusively expressed in gastric carcinoma cells, where its localization was found to be predominantly nuclear. However, in normal gastric mucosa, survivin was only expressed in stem cells located in the neck region of mucosa (Fig. 1). Sixty-three cases (40.1%) of gastric carcinoma in the present series were defined as positive. In immunohistochemical staining for p53 and Bax, 86 (54.8%) and 33 (21.0%) cases were positive, respectively (Fig. 2A and B). Survivin expression was not associated with p53 or Bax expression ($P = 0.29$ and 0.82, respectively).

Correlation Between Expression of Survivin and Clinicopathologic Factors

A clinicopathologic analysis of survivin-positive cases is shown in Table 2. As indicated, only tumor size was correlated with survivin expression in Stage III gastric cancer ($P < 0.05$). None of the other parameters, including patients' age, sex, differentiation, lymph node metastasis and lymphovascular invasion, was associated with positive expression of survivin.

Correlation Between Expression of Survivin and Prognosis of Stage III Gastric Cancer Patients

The cumulative 5-year survival rate for patients with all Stage III gastric cancer was 42.5%. The univariate analysis

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Table 2. Correlation between survivin expression and clinicopathologic factors

Variables	*n*	Survivin expression (%)	*P* value
Age (years)			
≤60	91	34 (37)	0.415
>60	66	29 (44)	
Gender			
Male	102	37 (36)	0.232
Female	55	26 (47)	
Tumor size (cm)			
≤5	63	16 (25)	0.003
>5	94	47 (50)	
Differentiation			
Differentiated	67	29 (43)	0.514
Undifferentiated	90	34 (38)	
Depth of tumor invasion			
pT2	49	20 (32)	0.906
pT3/T4	108	43 (40)	
Lymph node metastasis			
pN0/N1	58	21 (36)	0.502
pN2	99	42 (42)	
Lymphatic invasion			
Negative	12	4 (33)	0.764
Positive	145	59 (41)	
Vein invasion			
Negative	137	56 (41)	0.808
Positive	20	7 (13)	
Neural invasion			
Negative	50	19 (38)	0.73
Positive	107	44 (41)	
Lauren classification			
Intestinal	51	19 (37)	0.607
Diffuse	70	27 (39)	
Mixed	36	17 (47)	

showed that survivin and p53 expression was significantly correlated with survival time (Table 3). The survival rate of patients with survivin-positive cancer was significantly lower compared with that of patients with survivin-negative cancer (51.5% vs. 29.0%, respectively; $P < 0.05$) (Fig. 3A). Also, p53-positive cancer was associated with poorer prognosis (Fig. 3B). Multivariate analysis with logistic regression was performed on factors related to prognosis, and the expression of survivin and p53 was identified as independent predictive factors of poor prognosis (Table 4).

Table 3. Univariate analyses of prognostic factors for survival of Stage III gastric cancer patients

Variables	*n*	5-year survival rate (%)	*P* value
Age (years)			
≤60	91	49	0.075
>60	66	33	
Gender			
Male	102	44	0.871
Female	55	40	
Tumor size (cm)			
≤5	75	51	0.066
>5	82	37	
Differentiation			
Differentiated	67	37	0.472
Undifferentiated	90	47	
Lymph node metastasis			
pN0/N1	58	48	0.378
pN2	99	39	
Lymphatic invasion			
Negative	12	49	0.591
Positive	145	42	
Survivin expression			
Negative	99	52	0.006
Positive	58	29	
p53 expression			
Negative	71	52	0.046
Positive	86	35	
Bax expression			
Negative	124	40	0.395
Positive	33	52	

DISCUSSION

Gastric cancer is the second most common cause of death by cancer in Korea. Surgical resection remains the mainstay and only potentially curative treatment (18), but many patients eventually die of disease recurrence. Although the prognosis for Eastern patients with gastric cancer has been reported to be better compared with Western patients (19), the survival rate of patients with advanced gastric cancer has been dismal. Recently, we reported a 66% 5-year survival rate for all stage patients; however, the survival rates for those with stages IIIA and IIIB were only 34% and 10%, respectively (1). Although the pathologic tumor-node-metastasis stage and the possibility of curative surgery are the most powerful prognostic factors of gastric cancer, each patient with same stage gastric cancer has different risks of recurrence and

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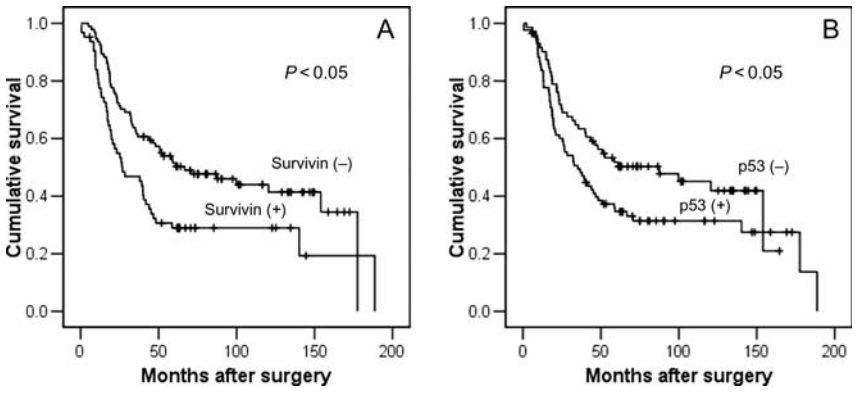

Figure 3. Survival curves for patients with Stage III gastric cancer according to the expression scores of surviving and p53. (A) The 5-year survival rates of patients with survivin-positive cancers were significantly lower compared with those with survivin-negative cancers ($P < 0.05$). (B) The 5-year survival rates of patients with p53-positive cancers were significantly lower compared with those with p53-negative cancers ($P < 0.05$).

Table 4. Clinicopathologic independent prognostic factors in Stage III gastric cancer patients (multivariate Cox regression analyses)

Variables	Hazard ratio (95% confidence interval)	*P* value
Tumor size (cm)		
≤5	1	0.207
>5	1.31 (0.860–2.009)	
Survivin expression		
Negative	1	0.027
Positive	1.68 (1.062–2.662)	
p53 expression		
Negative	1	0.036
Positive	1.55 (1.029–2.334)	

survival. Therefore, along with the development of more aggressive surgery and newer antineoplastic agents, efforts have been directed toward the identification of patients who have a higher risk of poor prognosis and the selection of patients who have a greater likelihood of responding to adjuvant treatments (20).

Survivin inhibits apoptosis by either directly or indirectly interfering with the function of effector caspase-3 and caspase-7 and also counteracts cell death by interfering with initiator caspase-9 processing. Survivin also counteract a default induction of apoptosis in G2/M phase (21). It associates with microtubules of the mitotic spindle in a specific and saturable reaction at the beginning of mitosis. The overexpression of survivin in cancer may overcome this apoptotic checkpoint and favour aberrant progression of transformed cells through mitosis. Overexpression of survivin was observed in all the most common human cancers, including colorectal, lung, uterus, esophageal, bladder and liver cancers. For gastric cancer, several studies showed the survivin expression rate between 34.5% and 82.0% of cancerous tissues by immunohistochemical analyses or RNA extraction (15,22). Despite some disagreement (23), several reports show that survivin expression is correlated with poor survival of patients and contributes to chemoresistance in gastric cancer (24). In our study, although the expression of survivin was observed in less than half of patients, it was significantly associated with poor survival. In addition, survivin expression was the independent prognostic factor for Stage III gastric cancer. This finding implies that more aggressive adjuvant treatment should be considered for patients with survivin-expressing advanced gastric cancer.

The p53 mutation is frequently seen in gastric cancer, and numerous studies have been published. Tumor-suppressor gene *p53* involves the apoptotic pathway by either intrinsic or extrinsic pathway, and abnormalities of p53 may indicate dysfunctional control of apoptosis and represent possible indices of malignancy (25). Although the prognostic impact of abnormal expression of p53 in gastric cancer patients remains controversial, recent reports indicate that p53 abnormality significantly affects cumulative survival (26). For the relation with survivin, one report showed that depletion of survivin caused defects in cell division, followed by an arrest of DNA synthesis due to the activation of a checkpoint involving the tumor-suppressor protein, p53 (27). In the present study, 54.8% of tumors expressed p53, and its expression was significantly correlated with patient's survival. Extranuclear p53 mediates apoptosis by interacting with Bcl-2 family members at mitochondria. p53 involves both the transactivation of Bax and the transcriptional repression of Bcl-2, and p53 can directly activate the pore-forming functions of Bax (28). It has been reported that Bax expression was associated with a better prognosis and was found to be a predictive marker for adjuvant chemotherapy (29).

However, there was no correlation between Bax and survivin expression or clinicopathologic parameters in our study. The present data indicate that p53 and Bax proteins are not correlated with survivin expression in gastric cancer. It is not certain why this discrepancy exists, although all these proteins may block the apoptotic pathway. Some authors suggest that survivin may be an independent prognostic marker not associated with p53 or Bax expression (30). In

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addition, survivin gene expression is transcriptionally repressed by wild-type p53 and can be deregulated in cancer by loss of p53 function (31). Because we did not examine p53 mutation, it is not certain whether a nuclear p53-positive case has mutation, or not. While p53 and Bcl-2 are involved in the modulation of cell progression and viability, other mediators of apoptosis may have a role. For example, expression of surviving in gastric cancer was associated with reduced apoptosis and COX-2 expression (32).

Ever since the role and prognostic significance of survivin in various cancers was discovered, several efforts have been made to develop survivin inhibitors for clinical use with the aim to inhibit tumor growth through an increase in spontaneous apoptosis and to enhance tumor cell response to apoptosis-inducing agents. Different kinds of survivin molecular antagonists, including antisense oligonucleotides, ribozymes, small-interfering RNAs and cancer vaccines, have been studied (33). It is necessary to investigate the possibility of clinical application of these inhibitors.

In conclusion, survivin expression is frequently observed in large-sized tumor and is an important prognostic indicator of poor outcome in Stage III gastric carcinoma. Patients with surviving-positive gastric cancer would be needed more intensive or novel therapies. And only well-designed controlled clinical trial can probe the significance of survivin in those studies.

Acknowledgments

The authors would like to thank Mrs Meryl R. Greenblatt (Editor, HPB Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY, USA) for critical review and medical editing.

Funding

This study was partly supported by The Catholic Cancer Center.

Conflict of interest statement

None declared.

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