

Immunohistochemical Study of p27^{Kip1} Expression in Gastric Adenomas and Early Gastric Carcinomas

- Analysis of 65 Cases -

Na-Hye Myong

Department of Pathology, Dankook
University College of Medicine,
Cheon-An, Korea

Received : July 29, 2003
Accepted : October 6, 2003

Corresponding Author

Na-Hye Myong, M.D.
Department of Pathology, Dankook University College
of Medicine, San 29, Anseo-dong, Cheon-An
330-714, Korea
Tel: 041-550-3891
Fax: 041-561-9127
E-mail: myongnh@dankook.ac.kr

*The present research was conducted by the research
fund of Dankook University in 2003.

Background : Recent studies have suggested that loss of p27^{Kip1} expression correlates with poor prognosis in gastric carcinomas, although the published data is still controversial. However, there are very few reports on the immunohistochemical expression of p27^{Kip1} in gastric adenomas and its significance in the progression of gastric adenomas to early gastric carcinomas (EGCs) is unclear. We therefore performed an immunohistochemical study for p27^{Kip1} expression in gastric adenomas with low- and high-grade dysplasia and EGCs to investigate the role of p27^{Kip1} expression in gastric carcinogenesis. **Methods :** We collected 45 cases of endoscopic mucosal resection specimens which were diagnosed as gastric adenomas and 20 cases of gastrectomy specimens showing EGCs. Using a monoclonal antibody against p27^{Kip1}, the immunohistochemistry was performed on paraffin-embedded specimens. **Results :** The loss of p27^{Kip1} immunoreactivity (<5% of the tumor cells) tended to be observed more frequently in high-grade adenomas than in the low-grade. The loss was found significantly higher in the EGCs than in both high-grade and low-grade adenomas ($p=0.000$). Gastric adenomas with villous component showed significant loss of p27^{Kip1} expression ($p=0.057$). **Conclusion :** These results suggest that loss of p27^{Kip1} expression can play a role in the progression of gastric adenomas into adenocarcinomas and the villous component allows reliable estimation of the possibility for malignant transformation.

Key Words : p27^{Kip1}-Immunohistochemistry-Stomach-Adenoma-Carcinoma

INTRODUCTION

Gastric adenoma is a circumscribed benign neoplasm composed of tubular or villous structures lined by dysplastic epithelium.^{1,2} The epithelial lining of gastric adenomas may be either the intestinal-type (containing goblet cells and/or Paneth cells) or the gastric-type (lined by gastric foveolar cells containing neutral mucin). The intestinal-type epithelium is most common in gastric adenomas.¹ This correlates with the extensively intestinalized and atrophic background gastric mucosa in many adenoma patients.³ This is in contrast to colonic adenomas, which often occur in a normal mucosal background.

The dysplasia in gastric adenomas is usually classified as either low-grade or high-grade, because this two-tiered grading system for dysplasia has become widely accepted due to its ease of use and high reproducibility.⁴ Adenomas with low-grade dysplasia showed elongated, hyperchromatic and crowded nuclei with mild pseudostratification. Cribriforming architecture, marked glandular

crowding, full-thickness nuclear stratification, and/or severe cytologic atypia were criteria for high-grade dysplasia. The propensity for unresected adenomas to give rise to gastric carcinomas has been well described, although the exact frequency of carcinomas arising within adenoma precursors has been reported to vary from 2.5% to >50%.⁵⁻⁷

p27^{Kip1} is a member of Cip/Kip family of cyclin-dependent kinase (cdk) inhibitors, which includes the p21, p27, and p57 protein. The p27^{Kip1} protein is present in quiescent cells, and the levels decrease when the cells are stimulated by growth factors.⁸ A decrease or an absence of p27^{Kip1} protein expression has been suggested to be a powerful negative prognostic marker in patients with various malignancies, including breast, colon, and esophageal cancers.⁸⁻¹⁰ Several studies also showed that a reduction in p27^{Kip1} protein level may reflect the progression of gastric carcinomas and might be an indicator of high-grade malignancy.¹¹⁻¹³ Although the immunohistochemical expression and the prognostic value of p27^{Kip1} have been studied relatively extensively in gastric car-

cinomas,¹¹⁻¹⁶ few studies on the p27^{Kip1} expression in gastric carcinogenesis including gastric adenomas and early gastric carcinomas (EGCs) have been performed.

This study aimed to evaluate p27^{Kip1} expression and clinicopathological characteristics in gastric adenomas including low- and high-grade adenomas and to elucidate the role of p27^{Kip1} expression and any significant clinicopathological factors in the evolution of gastric adenomas into EGCs.

MATERIALS AND METHODS

Specimens and histological evaluation

Between 1998 and 2002, 45 gastric adenomas in 43 patients, which were diagnosed based on a histological examination of forceps biopsy specimens, were treated by an endoscopic mucosal resection (EMR). For a comparison of several clinicopathological parameters and the immunoreactivity for p27^{Kip1} protein with those of gastric adenomas, 20 gastrectomy specimens of EGCs were included in this study. The endoscopy reports and photographs were reviewed to provide data on the size and location of the adenomas. The information on the size and location of the EGCs were obtained from the pathology reports.

The following clinical, endoscopic, and histological features of adenomas and EGC were evaluated in each patient: age, sex, size, number, location, presence of intestinal metaplasia in the lesions and in the surrounding mucosa, adenocarcinomas within the adenomas and in the nonpolypoid mucosa, and the presence of *Helicobacter pylori* (*H. pylori*) and atrophic gastritis in the surrounding mucosa. Adenomas were classified as being low-grade if they showed multiple, small, round, glandular structures lined by crowded elongated cells with hyperchromatic and mildly stratified nuclei. High-grade dysplasia was defined by the irregular tubular structures with branching architecture, glandular crowding, full-thickness nuclear stratification, and/or severe cytologic atypia. No degree of stromal invasion was allowed in this category. Carcinomas associated with gastric adenomas were classified as intratumoral, when an invasion into the lamina propria only or into the submucosa was detected.

Immunohistochemical staining and interpretation

Four- μ m-thick tissue sections were cut from formalin-fixed, paraffin-embedded blocks of 45 EMR specimens from gastric adenomas and 20 gastrectomy specimens, and placed on the silane-

coated slides. All the sections were deparaffinized through a series of xylene baths, and rehydrated through a graded series of alcohol. The sections were microwaved in 10 mM citrate buffer at 90°C for 10 min and were treated with a 3% H₂O₂-PBS solution to reduce the endogenous peroxidase activity. They were then incubated with normal bovine serum to reduce the nonspecific antibody binding and were subsequently subjected to the primary antibody reactions. The primary antibody used in this study was mouse anti-human-p27^{Kip1} monoclonal antibody (clone 57, Transduction Laboratories, Lexington, KY, USA) at a dilution of 1:500. After reaction with the primary antibody for 1 h at room temperature, the immunoreactive sites were detected by avidin-biotin-peroxidase complex method using a LSAB kit (DAKO). The sections were subjected to a color reaction with 3,3'-diaminobenzidine tetrahydrochloride containing 3% H₂O₂ in a Tris buffer and were lightly counterstained with Mayer's hematoxylin.

The immunostained cells for p27^{Kip1} were considered positive only when a distinct nuclear staining was identified. The level of immunoreactivity in gastric adenomas and EGCs was interpreted as having reduced or no p27^{Kip1} expression, if 5% or less of the tumor cell nuclei expressed p27^{Kip1}.

Statistical analysis

Several clinical and endoscopic parameters were analyzed by univariate and multivariate analyses between the low- and high-grade adenomas and between the high-grade adenomas and EGCs. In the univariate analysis, a student t-test was used to compare the patients' ages, and the other parameters were analyzed by a chi-square test. Several clinicopathological parameters were compared between two groups of gastric adenomas and the significance of difference was tested by a Fisher's exact test. The significance of difference in the reduced p27^{Kip1} expression among low- and high-grade groups of gastric adenomas and EGCs and between two categorical clinicopathological variables was analyzed by a Fisher's exact test. A p value ≤ 0.05 was considered statistically significant.

RESULTS

Clinical and endoscopic findings in gastric adenomas and early gastric carcinomas (Table 1 and 2)

Gastric adenomas occurred predominantly in males of both low- and high-grade groups. EGC patients also showed a male

predominance, with 14 males (70%) and 6 females (30%).

Adenomas were mainly distributed at the body and antrum of the stomach; body (23 polyps, 51.1%), antrum (14 polyps, 31.1%), angle (8 polyps, 17.7%). Most adenomas were solitary in 42 out of 45 cases (93.3%) and only 3 patients had two polyps each. EGCs showed an antral predominance (60%) in the location and solitary polyps in all 20 cases. The sizes of adenomas and EGCs were determined from the endoscopy and pathology reports, respectively, in all 65 cases and ranged from 0.4 to 4 cm in the adenomas and from 0.3 cm to 3.5 cm in the EGCs. A summary of the clinical and endoscopic findings in the 45 gastric adenoma cases and 20 EGC cases is shown in Table 1.

Table 1. Clinical and endoscopic findings in patients with gastric adenomas and EGCs

	Gastric adenomas		EGC (n=20)
	Low-grade (n=25)	High-grade (n=20)	
Gender distribution			
Female	7 (28%)	3 (15%)	6 (30%)
Male	18 (72%)	17 (85%)	14 (70%)
Age (mean ± SD)	63.0 ± 7.2	67.1 ± 8.6	58.2 ± 9.1
Location			
Body/fundus	16 (18) ^a (64%)	7 (35%)	7 (35%)
Antrum/pylorus	8 (9) ^a (32%)	6 (30%)	12 (60%)
Angle	1 (4%)	7 (35%)	1 (5%)
No. of lesions			
Single	22 (88%)	20 (100%)	20 (100%)
Multiple	3 (12%)	0	0
Size (cm)			
<0.5	(2) ^a	0	2 (10%)
0.5-<1	10 (11) ^a (40%)	3 (15%)	3 (15%)
1-<2	13 (52%)	7 (35%)	5 (25%)
2-<3	2 (8%)	7 (35%)	6 (30%)
≥3	0	3 (15%)	4 (20%)

^a: The number in parenthesis means the second data of the patients with multiple polyps. The number of polyps in all the cases with the multiple polyps is two. EGC: early gastric carcinoma, SD: standard deviation.

When univariate analysis was performed on the clinical and endoscopic parameters between the low- and high-grade adenomas, two of the variables listed in Table 1 -location and size- were found to have a statistically significant relationship with the grade of gastric adenomas. However, multivariate analysis (logistic regression method) showed that only the location was significantly associated with the degree of dysplasia in the gastric adenomas. In the univariate analysis between the high-grade adenomas and EGCs, age and location revealed a significant difference between the two groups. In the multivariate analysis, however, no significant difference in any parameters was found between them. The results of univariate and multivariate analyses are summarized in Table 2.

Clinicopathological findings within gastric adenomas and EGCs and background gastric mucosa (Table 3)

On histologic examination the majority of gastric adenomas and background mucosa showed intestinal metaplasia (97.7% and 95.5%), whereas only 45% of EGCs revealed it within the

Table 2. Results of univariate and multivariate analyses of clinical and endoscopic parameters

Parameters	Univariate analysis		Multivariate analysis	
	A	B	A	B
Age	0.092	0.003 ^a	0.110	0.375
Sex	0.473	0.451	0.117	0.357
Location	0.016 ^a	0.039 ^a	0.050 ^a	0.310
Number	0.242	UA	0.893	UA
Size	0.012 ^a	0.635	0.156	1.000

A: denotes comparison between low- and high-grade adenomas. B: denotes comparison between high-grade adenomas and early gastric carcinomas. UA: unavailable due to failure to analyze the data in the multivariate analysis. ^a: p value <0.05.

Table 3. Comparison of clinicopathologic findings among low-grade, high-grade gastric adenomas and EGCs

	Overall adenomas (n=45)	Low-grade adenomas (n=25)	High-grade adenomas (n=20)	EGCs (n=20)	p value ^a
Size < 2 cm	32 (71.1%)	23 (92%)	9 (45%)	10 (50%)	0.001
Antral/pyloric L.	14 (31.1%)	8 (32%)	6 (30%)	12 (60%)	1.000
Intestinal metaplasia					
Intratumoral	44 (97.7%)	25 (100%)	19 (95%)	9 (45%)	1.000
Surrounding	43 (95.5%)	24 (96%)	19 (95%)	20 (100%)	1.000
Adenocarcinoma					
Intratumoral	3 (6.6%)	0	3 (15%)		0.08
Surrounding	2 (4.4%)	2 (8%)	0		0.495
Villous component	9 (20%)	2 (22%)	7 (78%)		0.057
Surrounding mucosa					
<i>H. pylori</i> gastritis	5 (11.1%)	3 (12%)	2 (10%)	1 (5%)	1.000
Atrophic gastritis	22 (48.8%)	12 (48%)	10 (50%)	6 (30%)	1.000

^a: p value between low- and high- grade adenomas. EGC: early gastric carcinoma, L: location, *H. pylori*: *Helicobacter pylori*.

lesions. However, intestinal metaplasia was found in the background mucosae of all the EGCs. *H. pylori* gastritis in the background mucosa was detected in a small number of gastric adenoma and EGC cases (11.1% and 10%, respectively). Atrophic gastritis was more prominent than *H. pylori* gastritis in 48.8% and 30% of gastric adenomas and EGCs, respectively.

Malignant transformation within the gastric adenomas was found in 3 high-grade adenoma cases (15%), while the low-grade adenomas showed no adenocarcinoma (0%) within the lesions. However, surrounding mucosa disclosed 2 cases of adenocarcinomas only in the low-grade adenomas (8%) and not in the high-grade lesions. Those differences of intratumoral and surrounding adenocarcinomas between low- and high-grade adenomas, however, were not statistically significant. The gastric adenomas were classified into tubular and villotubular subtypes, based on the presence of villous component. The villotubular adenomas were found in only 9 of all 45 cases and a majority was found in the high-grade adenomas (7 cases). The villous component appeared to be significantly higher in the high-grade adenomas than the low-grade lesions ($p=0.057$).

Immunohistochemical expression for p27^{Kip1} in gastric adenomas and EGCs and its correlation with the clinicopathological variables in gastric adenomas (Table 4 and 5)

In the normal gastric mucosa, a distinct nuclear p27^{Kip1} expression was observed mainly in the normal lymphocytes in the lamina propria and occasionally in the foveolar epithelial cells (Fig. 1). Most low-grade adenoma cases (22 out of 25 cases, 88%) revealed a distinct nuclear positivity for the p27^{Kip1} protein in more than 5% of the tumor cells (Fig. 2).

The loss of p27^{Kip1} expression tended to appear more frequently in high-grade adenomas (Fig. 3) than in the low-grade lesions, although the difference was not statistically significant ($p=0.083$). EGCs showed loss of p27^{Kip1} expression in most cases (19 of 20

cases, 95%) (Fig. 4), which was significantly higher than the frequencies of both low- and high-grade adenomas ($p=0.000$). p27^{Kip1} expression was not dependent on the size of gastric adenoma, when the size criteria of 2 cm was applied to the p27^{Kip1} (-) and (+) groups ($p=1.000$). No significant difference in p27^{Kip1} expression was found between the *H. pylori* (+) and (-) groups. Adenomas with malignant transformation were more frequently p27^{Kip1} negative than pure gastric adenomas, with no statistically significant difference ($p=0.143$). On the other hand, the frequency of a reduced p27^{Kip1} expression was significantly higher in the villotubular adenomas than in the tubular adenomas ($p=0.002$).

DISCUSSION

The terms “gastric epithelial dysplasia” and “adenoma” refer to the architecture of the lesion formed by the dysplastic epithelium. These two types of lesion are classified as “noninvasive neoplasia” according to the Padova international classification.¹⁷ When the dysplastic epithelium forms a discrete macroscopic mass that protrudes into the lumen, it is classified as an adenoma. Recently, gastric adenomas are generally divided into low- and high-grade adenomas. The importance of classification into the two subtypes of low- and high-grade adenomas is based on the different risk of developing cancer between the two subcategories of gastric adenomas. A study by Park *et al.*¹⁸ revealed that high-grade dysplasia had a significant relationship with malignant transformation. In our study, overall adenomas showed malignant transformation in 3 out of 45 cases (6.6%), among which all were high-grade adenomas. No low-grade adenomas underwent a

Table 5. Correlation between immunohistochemical expression for p27 protein and clinicopathologic variables in 45 gastric adenomas

Clinicopathologic variables	p27		p value
	Negative	Positive	
Size of adenomas			
<2 cm	2 (25)	9 (75)	1.000
≥2 cm	7 (21)	26 (79)	
<i>H. pylori</i> infection			
Present	2 (40)	3 (60)	0.306
Absent	8 (20)	32 (80)	
Villous component			
Villotubular adenomas	6 (67)	3 (33)	0.002
Tubular adenomas	4 (12)	32 (88)	
Malignant transformation			
Adenoma with carcinoma	2 (66)	1 (34)	0.143
Adenomas	9 (21)	33 (79)	

H. pylori: *Helicobacter pylori*.

Table 4. Comparison of immunohistochemical expression for p27 protein among low- and high-grade gastric adenomas and EGCs

Lesions (No. of cases)	p27		p value
	Negative	Positive	
Low-grade adenomas (25)	3 (12%)	22 (88%)	* ^a
High-grade adenomas (20)	7 (35%)	13 (65%)	
EGCs (20)	19 (95%)	1 (5%)	

*^a: 0.083. **^b: 0.000, between low-grade adenomas and EGCs or between high-grade adenomas and EGCs. EGC: early gastric carcinoma.

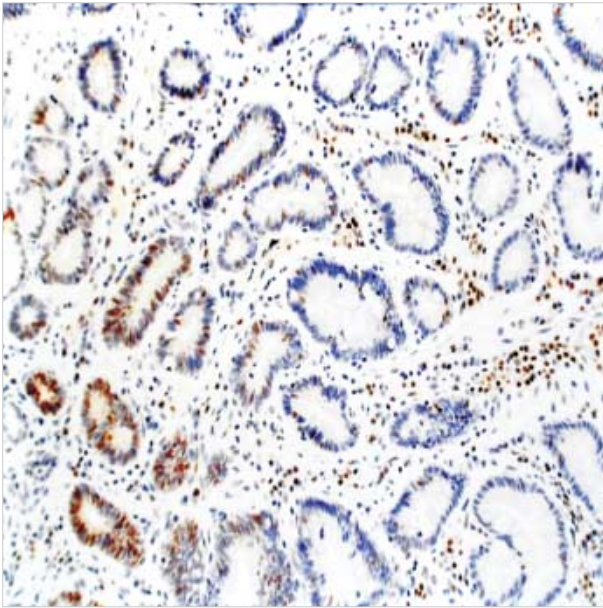


Fig. 1. Immunohistochemical staining p27 in normal gastris mucosa reveals distinct nuclear positivity in the lymphocytes of lamina proria and occasionally in the foveolar epithelial cells.

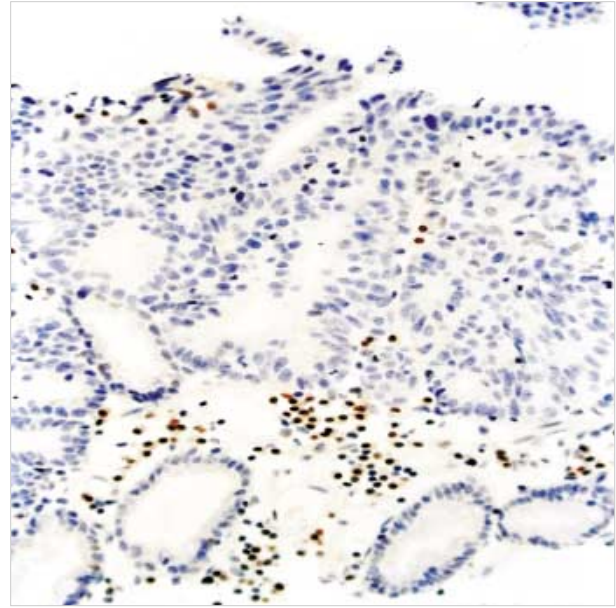


Fig. 3. High-grade gastric adenoma discloses loss of p27 expression by p27 immunopositivity in less than 5% of the nuclei of the adenoma cells.

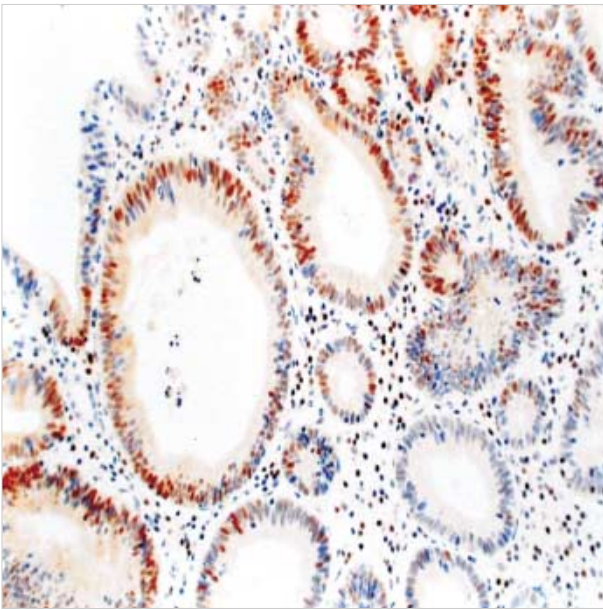


Fig. 2. Low-grade gastric adenoma shows p27 nuclear immunopositivity in the cells more than 5%.

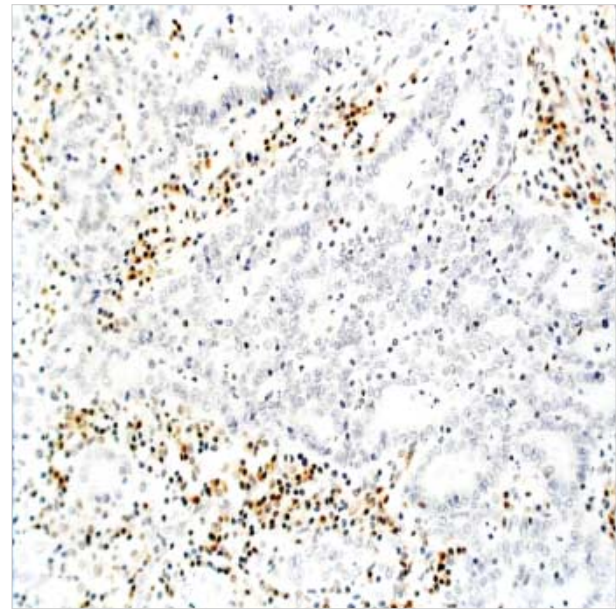


Fig. 4. Early gastric adenocarcinoma reveals no p27 immunoreactive nuclei in contrast to the adjacent normal lymphocytes in the lamina propria.

malignant transformation. High-grade adenomas showed a higher tendency for malignant transformation than low-grade ones (15% versus 0%), although the difference in the rates of malignant change between them was not statistically significant ($p=0.08$). In the literature, the incidence of carcinomas arising within adenomas reported varies considerably from 2.5% to >50%⁵⁻⁷ and

also synchronous gastric carcinomas have been reported in gastric adenomas with varying frequencies, ranging from 8% to 59%.¹⁸ In the current study, synchronous cancers were found in only 2 cases of low-grade adenomas (8%).

The epidemiological and histopathological studies pioneered by Correa¹⁹ showed that a gastric cancer of the intestinal type

frequently develops through a sequence of histological events: diffuse chronic gastritis, often mucosal atrophy, intestinal metaplasia, dysplasia, and finally invasive carcinoma. Gastric dysplasia usually develops in the setting of intestinal metaplasia (usually of incomplete type), although it may also occur in apparently normal mucosa.²⁰ Several prospective and retrospective serologic studies have now linked *Helicobacter pylori* (*H. pylori*) infection to gastric cancer.^{21,22} *H. pylori* infection is clearly associated with the induction of chronic inflammation of the gastric mucosa and the progressive development of metaplastic changes. This study also investigated the occurrence of intestinal metaplasia (IM), *H. pylori* infection, and atrophic gastritis in the mucosa surrounding the low- and high-grade gastric adenomas. Both subtypes of gastric adenomas similarly revealed a very high incidence of IM (95% and 96%), whereas *H. pylori* infection was relatively rarely found in both of them (12% and 10%). Atrophic gastritis was found to be moderately high in both subtypes (48% and 50%). This much lower incidence of *H. pylori* infection compared to that of IM and atrophic gastritis might be interpreted that *H. pylori* organisms cannot colonize the metaplastic epithelia since they lack the necessary bacterial adhesion factors.²³ EGCs showed a similar tendency for those results with the gastric adenomas, but IM within the tumor lesions occurred much less frequently in EGCs than in gastric adenomas (45% versus 95-100%).

p27^{Kip1} is a cyclin-dependent kinase inhibitor, inhibiting the G1 to S transition by binding to the complexes of G1 cyclins and cyclin-dependent kinases thereby preventing the progression of the cell cycle.²⁴ Loss of p27^{Kip1} has been described to correlate with the factors associated with an aggressive tumor behavior in gastric carcinoma, although the results are still controversial. Several studies reported that a loss of p27^{Kip1} was an independent predictor of a poor survival in multivariate analyses. The studies mentioned above found a correlation between the p27^{Kip1} expression and the clinicopathological parameters such as the depth of invasion, a lymph node metastasis, a poorly differentiated histology, a diffuse type of tumor, and a lymphatic invasion.^{12,13} On the other hand, another studies have reported that there was no correlation between the level of p27^{Kip1} expression and the survival or variable prognostic parameters in gastric carcinomas.¹⁴⁻¹⁶

In comparison to the studies for p27^{Kip1} expression in gastric carcinomas, those in gastric adenomas and/or gastric carcinogenesis are very few. A study reported by Oya *et al.*²⁵ showed that a low p27^{Kip1} expression was considered to be a great value for estimating the dysplastic progression of gastric adenomas into carcinomas, because the frequency of a low p27^{Kip1} expression in the carcinoma lesions was higher than in low- and high-grade ade-

noma lesions. In our study, we applied the different criteria for the interpretation of reduced p27^{Kip1} expression (<5% of tumor cells) from that of the previous study by Oya *et al.*²³ (<50 % of tumor cells), but the p27^{Kip1} expression was reduced progressively from the low-grade to high-grade adenomas and then to EGCs (12%, 35%, and 95%), too. The high-grade adenomas revealed a tendency for the p27^{Kip1} expression to be lower than in the low-grade adenomas, although the difference between them was not statistically significant ($p=0.083$). EGCs showed a significantly reduced p27^{Kip1} expression compared to both low- and high-grade adenomas ($p=0.000$). We thus guessed that the loss of p27^{Kip1} expression play a role in the progression of gastric adenomas into carcinomas.

It is known that adenomatous polyps with a diameter of 2 cm or more have been regarded as having a malignant potential.²⁶ However, another study reported that 75% of adenomas smaller than 2 cm showed focal carcinomas.¹⁸ When we applied the size criteria of 2 cm to the p27^{Kip1} expression, it was not dependent on the size of gastric adenomas. Therefore, we consider that it is likely that even small adenomas less than 2 cm in diameter still have a potential to be malignant, which could have an influence on the p27^{Kip1} expression. The malignant potential of a gastric adenoma is generally believed to be dependent on its histological composition. As with adenomas of the colon, most cancers developed in villous rather than tubular adenomas.^{18,27} In the current study, 3 adenomas showed the foci of adenocarcinoma within the polyps, and two of them were the villotubular types. When we also compared the p27^{Kip1} expression between the adenomas showing a villous component and those showing tubular component only, the loss of p27^{Kip1} expression was found more frequently in the villotubular adenoma groups ($p=0.002$). Gastric cells chronically exposed to *H. pylori* infection have been reported to be resistant to apoptosis and express reduced amounts of p27^{Kip1}.²⁸ Our results, however, showed that there was no significant difference of loss of p27 expression between *H. pylori* (+) and (-) groups ($p=0.306$).

Decrease of p27^{Kip1} is reported to be due to post-translational degradation of produced p27^{Kip1} protein by the ubiquitin-proteasome pathway and not due to the reduced synthesis of the p27^{Kip1} protein.²⁹ Mutations as the reason for decreased p27^{Kip1} levels in cancer cell nuclei are rare.³⁰ Therefore, immunohistochemistry appears to be a viable method for assessing the p27^{Kip1} expression in neoplasia. Our results also showed that the loss of p27^{Kip1} expression could be used as an important diagnostic indicator for the malignant potential of gastric adenomas in the gastric biopsy specimens.

In summary, high-grade adenomas tended to show higher frequency of both the carcinomatous change and loss of p27^{Kip1} expression than low-grade adenomas. EGCs revealed a much more frequent loss of p27^{Kip1} expression than both grades of adenomas. The villous component in the gastric adenomas induced a significant loss of p27^{Kip1} expression, whereas the size and *H. pylori* infection didn't. These results suggest that a loss of p27^{Kip1} expression can play a role in the disease progression of gastric adenomas into carcinomas or to a degree of low-grade into high-grade gastric adenomas. In addition, the villous component in gastric adenomas could be indicative of the possibility of malignant change associated with the loss of p27^{Kip1} expression.

REFERENCES

1. Abraham SC, Montgomery EA, Singh VK, Yardley JH, Wu T-T. Gastric adenomas. Intestinal-type and gastric adenomas differ in the risk of adenocarcinoma and presence of background mucosal pathology. *Am J Surg Pathol* 2002; 26: 1276-85.
2. Goldstein NS, Lewin KJ. Gastric epithelial dysplasia and adenoma: historical review and histological criteria for grading. *Hum Pathol* 1997; 28: 127-33.
3. Nakano H, Persson B, Slezak P. Study of the gastric mucosal background in patients with gastric polyps. *Gastrointest Endosc* 1990; 36: 39-42.
4. Misdraji J, Lauwers GY. Gastric epithelial dysplasia. *Semin Diag Pathol* 2002; 19: 20-30.
5. Nakamura K, Sakaguchi H, Enjoji M. Depressed adenoma of the stomach. *Cancer* 1988; 62: 2197-202.
6. Sakurai S, Sano T, Nakajima T. Clinicopathologic and molecular biologic studies of gastric adenomas with special reference to p53 abnormality. *Pathol Int* 1995; 45: 51-7.
7. Ito H, Yokozaki H, Ito M, Tahara E. Papillary adenoma of the stomach. Pathologic and immunohistochemical study. *Arch Pathol Lab Med* 1989; 113: 1030-4.
8. Porter PL, Malone KE, Heagerty PJ, *et al.* Expression of cell-cycle regulators p27^{Kip1} and cyclin E, alone and in combination, correlate with survival in young breast cancer patients. *Nat Med* 1997; 3: 222-5.
9. Tenjo T, Toyoda M, Okuda J, *et al.* Prognostic significance of p27 (Kip1) protein expression and spontaneous apoptosis in patients with colorectal adenocarcinomas. *Oncology* 2000; 58: 45-51.
10. Shamma A, Doki Y, Tsujinaka T, *et al.* Loss of p27 (Kip1) expression predicts poor prognosis in patients with esophageal squamous cell carcinoma. *Oncology* 2000; 58: 152-8.
11. Yasui W, Kudo Y, Semba S, Yokozaki H, Tahara E. Reduced expression of cyclin-dependent kinase p27^{Kip1} is associated with advanced stage and invasiveness of gastric carcinomas. 1997; 88: 625-9.
12. Kim DH, Lee HI, Nam ES, *et al.* Reduced expression of the cell-cycle inhibitor p27^{Kip1} is associated with progression and lymph node metastasis of gastric carcinoma. *Histopathology* 2000; 36: 245-51.
13. Ohtani M, Isozaki H, Fujii K, *et al.* Impact of the expression of cyclin-dependent kinase inhibitor p27^{Kip1} and apoptosis in tumor cells on the overall survival of patients with non-early stage gastric carcinoma. *Cancer* 1999; 85: 1711-8.
14. Wiksten JP, Lundin J, Nordling S, Kokkola A, von Boguslawski K, Haglund C. The prognostic value of p27 in gastric cancer. *Oncology* 2002; 63: 180-4.
15. Muller W, Grabsch H, Takeno S, Noguchi T, Hommel G, Gabbert HE. Prognostic value of the cyclin-dependent kinase inhibitor p27^{Kip1} in gastric cancer. *Anticancer Res* 2000; 20: 1787-92.
16. Feakins RM, Mulcahy HE, Quaglia A, Jawhari A, Zhang Z, Patchett SE. p27(Kip1) loss does not predict survival in patients with advanced gastric carcinoma. *Cancer* 2000; 89: 1684-91.
17. Rugge M, Correa P, Dixon MF, *et al.* Gastric dysplasia: The Padova international classification. *Am J Surg Pathol* 2000; 24: 167-76.
18. Park DI, Rhee PL, Kim JE, *et al.* Risk factors suggesting malignant transformation of gastric adenoma: Univariate and multivariate analysis. *Endoscopy* 2001; 33: 501-6.
19. Correa P. Clinical implications of recent developments in gastric cancer pathology and epidemiology. *Semin Oncol* 1985; 12: 2-10.
20. Ming SC. Cellular and molecular pathology of gastric carcinoma and precursor lesions: A critical review. *Gastric Cancer* 1998; 1: 31-50.
21. Talley NJ, Zinsmeister AR, Weaver A, *et al.* Gastric adenocarcinoma and *Helicobacter pylori* infection. *J Natl Cancer Inst* 1991; 83: 1734-9.
22. Parsonnet J, Friedman GD, Vandersteen DP, *et al.* *Helicobacter pylori* infection and the risk of gastric carcinoma. *N Engl J Med* 1991; 325: 1127-31.
23. Fenoglio-Preiser CM, Noffsinger AE, Stemmermann GN, Lantz PE, Lstrom MB, Rilke FO. *Gastrointestinal pathology. -An atlas and text* 2nd ed. Philadelphia: Lippincott Williams & Wilkins, 1999; 177.
24. Toyoshima H, Hunter T. p27, a novel inhibitor of G1 cyclin-Cdk protein kinase activity is related to p21. *Cell* 1994; 78: 67-74.
25. Oya M, Takashi Y, Tsuneyoshi M. Expressions of cell-cycle regulatory gene products in conventional gastric adenomas: Possible immunohistochemical markers of malignant transformation. *Hum Pathol* 2000; 31: 279-87.
26. Tomasulo J. Gastric polyps: histologic types and their relationships to gastric carcinoma. *Cancer* 1971; 27: 1346-55.
27. Orlowska J, Jarosz D, Pachlewski J, Butruk E. Malignant transformation of benign epithelial gastric polyps. *Am J Gastroenterol* 1995; 90: 2152-9.

28. Shirin H, Sordillo EM, Koelvska TK, *et al.* Chronic *Helicobacter pylori* infection induces an apoptosis-resistant phenotype associated with decreased expression of p27 (Kip1). *Infect Immuno* 2000; 68: 5321-8.
29. Pagano M, Tam SW, Theodoras AM, *et al.* Role of ubiquitin-proteosome pathway in regulating abundance of the cyclin-dependent kinase inhibitor p27. *Science* 1995; 269: 682-5.
30. Ponce-Castaneda MV, Lee MH, Latres E, *et al.* p27Kip1: chromosomal mapping to 12p12-12p13.1 and absence of mutations in human tumors. *Cancer Res* 1995; 55: 1211-4.