p27 expression and gastric carcinoma

To the editor — A cyclin-dependent kinase inhibitor, $p27^{Kip1}$, regulates progression from G1 into S phase. We read with great interest that the decrease or absence of p27 protein expression is a powerful negative prognostic marker in patients with breast[1] and colorectal carcinomas[2] and is a significant predictor of poor disease-free survival in patients with breast carcinoma[3]. Gastric carcinoma is the most common neoplasm in Japan and we therefore evaluated p27 expression in gastric carcinoma.

One hundred thirty-eight Japanese patients with primary gastric carcinomas were studied. Complete clinical and histopathologic data was available in these patients. Formalin-fixed, paraffin-embedded 5 μm thick sections were prepared. Immunohistochemical staining was performed as described previously[3]. p27 scoring was determined by observing 1000 cancer cells in at least ten high-power fields and scoring was independently determined by two observers. p27 scoring was classified as high (staining in > 50% of cells) or low (staining in ≤ 50% of cells). Negative controls using mouse immunoglobulin instead of primary antibody revealed no staining.

Eight six (62%) tumors were in the p27-low group and 52 (38%) tumors were in the p27-high group. In a number of cases the distribution of p27 positive cells within a tumor was not homogeneous; the p27-negative cells were more frequently seen in the advancing margin of the cancer compared with the other areas. The inter-observer agreement was 88.4%, indicating good reproducibility.

The correlation between p27 expression and aggressiveness of gastric carcinomas was examined. There were significant differences between p27-high and p27-low groups with respect to tumor size, depth of tumor invasion, lymph nodes metastasis, stage of the disease and curability (see Table). The 5-year survival was 18.3% in the p27-low group and 59.2% in the p27-high group, representing a significant difference ($p<0.01$). With respect to stage II and III, the 5-year survival was 27.4% and 69.1% in the p27-low and p27-high groups, respectively, a significant difference ($p<0.01$).

A multivariate analysis with Cox regression analysis was performed in 92 patients who had undergone curative operations to determine which covariates had the most prognostic significance with regard to survival. The analysis revealed that p27 status, depth of tumor invasion and lymph node metastasis were independent prognostic factors after curative resection for patients with gastric carcinoma (Table).

Clinicopathologic data and statistical analysis

	p-27 high (n = 52)	p-27 low (n = 86)	p-value
a, Tumor size (cm)	5.7 + 3.5	8.8 + 4.2	<0.01
Depth of invasion			
within the wall	24	20	<0.01
beyond the wall	28	66	
Lymphatic permeation			
absent	23	29	NS
present	29	57	
Vascular permeation			
absent	45	65	NS
present	7	21	
Lymph node metastasis			
absent	27	21	<0.01
present	25	65	
Stage			
I	16	7	<0.01
II	11	8	
III	16	28	
IV	9	43	
Curability of operation			
Curative	43	49	<0.01
Non-curative	9	37	
b, Cox regression analysis p value relative risk			
p27 status	<0.01	2.64	
Depth of tumor invasion	<0.01	2.22	
Lymph node metastasis	<0.01	1.69	

The following variables were used in the multivariate analysis: age, sex, tumor size, tumor location in the stomach, histologic type (intestinal type or diffuse type), gross type (circumscribed type or infiltrative type), depth of tumor invasion, lymphatic permeation, vascular vessel permeation and lymph node metastasis.

Our findings demonstrate that p27 expression status is an independent prognostic factor for patients with gastric carcinoma as well as those with breast or colon carcinoma. To better determine the clinical utility of p27 as a prognostic marker, we addressed the three points raised by Steeg and Abrams in their recent *News & Views*[4]. First, p27 status gives information independent of conventional pathologic factors. Second, p27 status gives significant information on survival of patients with stage II and III disease, including both potentially curative and non-curative patients. Finally, the examination of p27 status is reproducible.

In the absence of a standardized p27 assay and a better understanding of the mechanism by which p27 is down-regulated, more work is required before p27 expression status can be used in a routine clinical setting. However, at present 593 we consider that it may be useful as a major prognostic factor in many kinds of tumors.

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