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Expression Levels of Cyclin G2, But Not Cyclin E, Correlate With Gastric Cancer Progression[1]

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Purpose. **Cyclin G2 and cyclin E are important cell-cycle regulators in various cancer tissues. However, little is known about cyclin G2 expression in human gastric cancer tissues, and the role of cyclin E is quite controversial. This study evaluated their clinical significance in gastric cancer tissues.**

Materials and methods. **Immunohistochemical staining using the tissue array method was performed on 166 human gastric carcinomas. The clinicopathological features and prognostic significance were analyzed.**

Results. **Cyclin G2 and cyclin E expressions were positive in 110 (66.3%) and 77 (46.4%) human gastric cancer tissues, respectively. The incidence of cyclin G2 positivity was lower in females and in cancers with the undifferentiated type of histology. Moreover, cyclin G2 expression was inversely correlated with the more advanced stages ($P < 0.05$), the presence of lymph-node metastasis ($P < 0.05$), and the presence of perineural invasion ($P < 0.05$). However, no significant correlation was observed between the expression of cyclin E and all of the clinicopathological factors examined. Cyclin G2 expression was associated with a better overall survival (OS; 5-y OS, 50.6% for cyclin G2-positive *versus* 35.0% for cyclin G2-negative; $P < 0.05$). However, multivariate analysis revealed lymph-node metastasis, distant metastasis, and lymphatic invasion to be independent prognostic factors but not cyclin G2 expression.**

Conclusion. **Our study could not demonstrate any significant relationship between cyclin E expression and the clinicopathological variables. However, cyclin G2 appears to be a negative cell-cycle regulator in gastric cancer, and its expression seems to be inversely related to gastric cancer progression.**

Key Words: **gastric cancer; cyclin G2; cyclin E; immunohistochemistry.**

INTRODUCTION

Although the mortality rate of gastric cancer has decreased recently, it is still one of the leading causes of cancer death worldwide and the most commonly developed cancer in Korea.

Multiple genetic and epigenetic changes occur during the carcinogenesis process, and changes in the variable tumor suppressor genes or oncogenes can affect cell cycle control causing deregulated cell proliferation [1]. Through the cell cycle, various points react to external signals, such as growth factors, cellular adhesion, and stress, and to internal signals, such as damaged DNA and mitotic spindle formation. Using these checkpoints, the cell can ensure the order of events in the cell cycle and respond to DNA damage by halting cell-cycle progression or by undergoing programmed cell death [2, 3]. As cell cycle regulators, cyclin-dependent kinase (CDK) and cyclin-dependent kinase inhibitor (CKI) form protein complexes with cyclin, and their activities are essential for cell cycle progression [4]. The altered expression of variable cyclins is associated with the deregulation of the cell cycle and the uncontrolled cell proliferation in cancer cells.

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Several types of cyclins have been identified in mammalian cells with most promoting cell cycle progression and, subsequently, cancer cell proliferation. Especially, cyclin E is one of the most important cell cycle regulators, and its deregulations are known to be general events in various types of cancers. However, the role of cylcin E in gastric cancer is quite controversial.

Cyclin G2 is a newly identified homologue of cyclin G1, and in contrast to conventional cyclins, is known to induce cell cycle arrest and be up-regulated when the cells undergo arrest or apoptosis. Its down-regulation has been reported in papillary carcinomas of the thyroid, breast cancer, and oral cancer [5–7]. However, its role in gastric cancer is still unclear.

The present study investigated the patterns of cyclin G2 and cyclin E expressions in human gastric cancer tissues and evaluated the clinicopathological features according to their expressions. The prognostic significance was also analyzed for each indicator, including cyclin G2 and cyclin E.

PATIENTS AND METHODS

Patients

Data were collected retrospectively on 166 patients undergoing surgery for gastric cancer at the Department of Surgery, Samsung Medical Center between September 1994 and December 1997. Their tumor specimens and the tissues of normal mucosa (7 cases) and intestinal metaplasia (4 cases) had been banked and examined using an Institutional Review Board-approved protocol. The patients' characteristics and pathologic findings were reviewed retrospectively from the medical records and pathology reports, respectively. The study group consisted of 95 men and 71 women with a median age and median follow-up duration of 56.7 y (range, 23–81 y) and 35.7 mo (range, 0.4–146.2 mo), respectively. None of those patients received preoperative chemo- or radiotherapy. Adjuvant chemotherapy was routinely prescribed for all patients with advanced gastric cancer. The histological types were divided into two subgroups: the differentiated type, which consisted of well- and moderately differentiated adenocarcinoma, and the undifferentiated type, which consisted of a poorly differentiated adenocarcinoma, signet ring cell carcinoma, and mucinous carcinoma. Staging was carried out according to the AJCC Cancer Staging Manual (6th edition, 2002) [8]. The survival data were obtained from the patients' medical records and the Korean cancer registry.

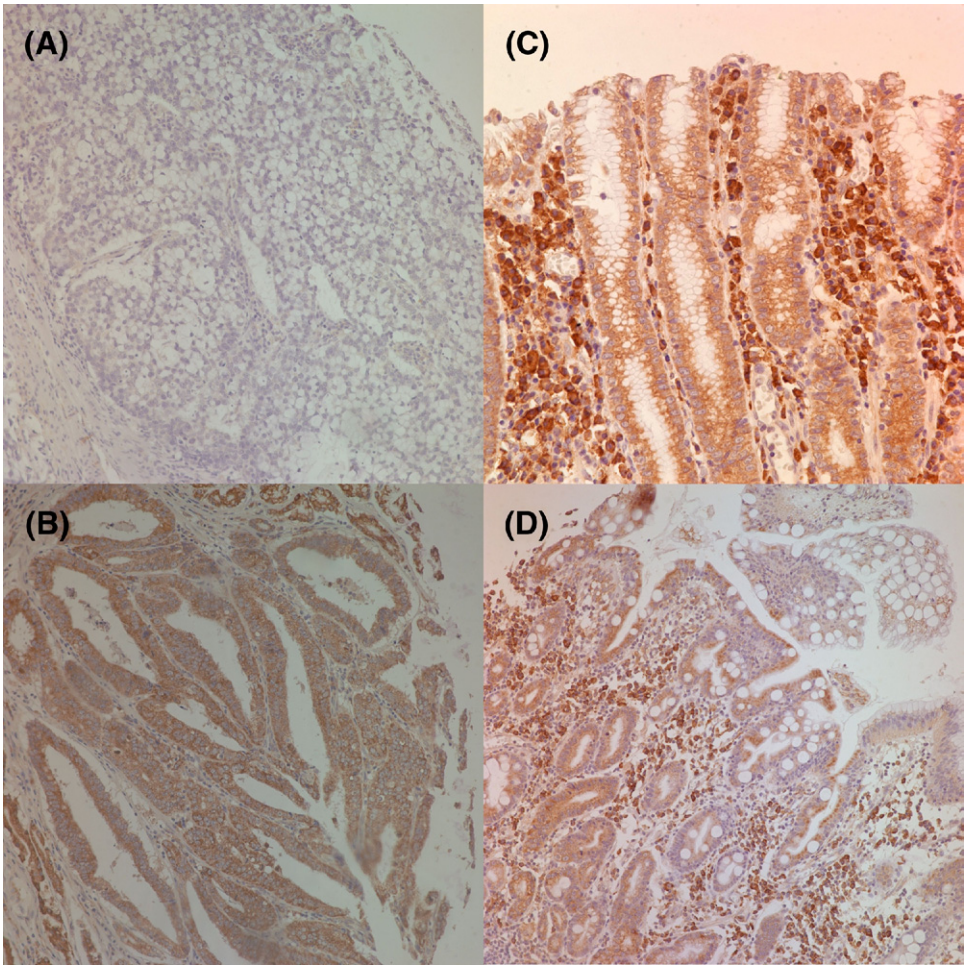

FIG. 1. Typical results of cyclin G2 immunohistochemical staining (200×). (A) No cyclin G2 expression was found in the poorly differentiated cancer tissues. Positive expression of cyclin G2 was detected in the tissues of well differentiated type cancer (B) normal mucosa (C), and intestinal metaplasia (D). (Color version of figure is available online.)