JBUON 2017; 22(2): 383-389
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

E-cadherin in gastric carcinomas: Relations with histological parameters and its prognostic value

Dimitrios Schizas[1,3], Demetrios Moris[2], Adamantios Michalinos[3], Prodromos Kanavidis[1], Dimitrios Oikonomou[3], Alexandros Papalampros[3], Anastasios Machairas[1], Theodoros Liakakos[1,3]

[1]3rd Department of Surgery, "Attikon" General Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece; [2]Department of Immunology, Lerner Research Institute, Cleveland Clinic, Cleveland, Ohio, USA; [3]1st Department of Surgery, "Laikon" General Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece

Summary

Purpose: *Gastric cancer (GC) is still one of the most common malignancies with the majority of the tumors being diagnosed at advanced stage. The need for identification of prognostic and early detection biomarkers is thus compulsory. E-cadherin is one of the emerging biomarkers that is currently evaluated in the literature in the frame of epithelial-mesenchymal transition (EMT). Our aim was to study the expression of E-cadherin in the various histological subtypes of GC and to evaluate its prognostic value.*

Methods: *This historical cohort survey was performed on gastric tumors obtained from 66 (46 men and 20 women) patients with documented gastric adenocarcinoma who underwent total or partial gastrectomy and regional lymphadenectomy from 2003 till 2011. Features such as tumor size, depth of invasion, grade and histological subtype, lymphovascular space invasion and regional lymph nodes involvement were also evaluated. Immunohistochemistry (IHC) was used for assessing the expression of E-cadherin with a semi-quantitative model.*

Results: *The correlation of E-cadherin tissue expression with patient overall survival (OS) or disease-free survival (DFS) was not statistically significant, as well as with gender, T stage, N stage, TNM stage, grade, positive lymph nodes ratio or lymphovascular invasion.*

Conclusions: *73.0% of the evaluated tumors showed abnormal E-cadherin expression in IHC, but the correlation of E-cadherin tissue expression with patient OS or DFS was not statistically significant. Literature stands equivocal about the association between E-cadherin gene mutation, and histopathology and tumor invasiveness. Our results further strengthen the need of larger studies to fully elucidate the predictive role of E-cadherin in the natural history of GC.*

Key words: *E-cadherin, epithelial-mesenchymal transition, gastric adenocarcinoma, immunohistochemistry, survival*

Introduction

Despite the emerging data that indicate a declining incidence and mortality, GC is still one of the most common malignancies in the world causing around 738,000 deaths worldwide [1]. Unfortunately the majority of these cancers at the time of diagnosis are at advanced stage and the treatment options are limited. Invasion and metastasis, the major causes of GC-related relapse and death, greatly impede the treatment efficiency [2]. A better understanding of the mechanism contributing to GC initiation and progression is warranting with the hope to improve early diagnosis and treatment efficacy. Thus, the need for identification of prognostic and early detection biomarkers, possessing predictive value for survival of GC patients, is compulsory [3].

Correspondence to: Demetrios Moris, MD, MSc, PhD, MACS. Lerner Research Institute, Cleveland Clinic, 9500 Euclid Ave., NE60, Cleveland, Ohio 44195, USA. Tel: +1 (216) 444-2574, Fax: +1 (216) 445-4658, E-mail: dimmoris@yahoo.com,
Received: 13/09/2016; Accepted: 24/09/2016

One of the emerging biomarkers that is currently evaluated in the literature is E-cadherin. E-cadherin gene is a tumor suppressing gene, expressing E-cadherin transmembrane glycoprotein, which plays a significant role in adhesion and differentiation of epithelial cells [4,5]. Mutation in E-cadherin gene may lead to dysfunction in cell adhesion and is correlated with more invasive and aggressive malignant behaviors [4,5] as it is associated with the prognosis of GC patients [6,7].

Literature has also focused on EMT, a process where epithelial cells are transformed into cells of mesenchymal phenotype, highly expressing invasive and migratory properties. Tumor microenvironment consisting of tumor stromal cells and growth factors, modulate cancer cell growth and regulate their malignant behavior via EMT induced by diverse intracellular signaling pathways which alter modes of transcription and translation that, in turn, could regulate malignant cell behavior directly and indirectly via modulating the microenvironment [8]. Detailed investigation into the role of EMT in GC could further drive our understanding of GC initiation, invasion and metastasis.

Since Oka et al. [9] initially reported that GC tissues exhibited heterogeneous E-cadherin expression patterns, the prognostic role of reduced E-cadherin expression has been widely explored, due to the observation that these findings had more and more clinical relevance. Although a large number of studies were performed on patients with GC, the prognostic value of E-cadherin for GC patients remains controversial, and numerous studies published in this field include a small number of cases. We thus conducted this study to evaluate the prognostic significance of E-cadherin expression in patients with GC. More specifically, the aim of this study was to investigate the association between alteration in E-cadherin expression and histopathological characteristics of gastric adenocarcinoma in patients who had undergone resection operations.

Methods

Participants

This historical cohort survey was performed on gastric tumors obtained from 66 patients (46 men and 20 women) with documented gastric adenocarcinoma who underwent total or partial gastrectomy and regional lymphadenectomy in the 3rd Department of Surgery, "Attikon" General Hospital, National and Kapodistrian University of Athens, Athens, Greece, in 2003-2011. Gastric tumors other than adenocarcinoma were not included in the study. The study was approved by the ethics committee of "Attikon" General Hospital, National and Kapodistrian University of Athens, Athens, Greece. No patient had received neoadjuvant therapy (neither chemotherapy nor radiotherapy). Information about age and gender were obtained from the patient records. Histopathological characteristics of the tumor, such as depth of tumor invasion, grade, histological subtype according to Lauren classification, vascular, lymphatic and regional lymph nodes involvement were extracted from the pathology reports. TNM staging was performed according to the American Joint Committee on Cancer Staging Manual 7th edition. Tissue blocks were extracted from the surgical specimen and subjected to IHC.

All involved persons (subjects or legally authorized representatives) gave their informed consent (written or verbal, as appropriate) prior to study inclusion.

Immunohistochemistry

IHC was used for assessing the expression of E-cadherin. One 4-μm-thick section was cut from 1 representative paraffin block of each case. The sections were floated onto salinized glass slides and dried out at 37°C overnight, and then kept in 60°C for 1 hr, before de-paraffinization in xylene and rehydration through graded ethanol. All sections were subjected to microwave heating at 850 W for 22 min in pH 6.0 citrate buffer and cooled in running water. Antibody used was E-cadherin clone CL NCH-38 (Dako, Poland), dilution 1:50 at room temperature. IHC staining was carried out using a HRP polymer detection envision method (Dako, EnVision+System, Poland). Diaminobenzidine (DAB) was used as chromogen and sections were counterstained with Harris' hematoxylin. Appropriate positive and negative controls omitting the primary antibodies were included with each slide run.

Evaluation of samples

Protein expression was assessed using the widely accepted HSCORE system. The HSCORE was calculated using the following equation: HSCORE = $\sum Pi(I)$ (I = 0, 1, 2, 3, Pi = 0–100%), where I represents the staining intensity, i.e., 0=no staining, 1=weak staining, 2=moderate staining, and 3=strong staining, and Pi represents the percentage of stained cells with intensities varying from 0 to 100%. The final HSCORE varied from 0 to 300 and E-cadherin expression levels were classified as negative and positive with a cutoff value of 30 [10].

Statistics

Statistical analysis was carried out using R language and environment for statistical computing (http://www.R-project.org). To describe data, we used mean±standard deviation, median (range), frequency, whereas x^2 test, Fisher's exact test, Student's or Welch's t-test and Wilcoxon rank-sum test were used, where appropriate, to compare results between groups. The Kaplan–Meier method was used to estimate the overall survival (OS) rate, and survival differences were ana-

Table 1. Clinicopathological patient characteristics and correlation with overall survival and disease-free survival (log-rank p value)

Characteristics	*Age, years, mean (±SD)*	*Number of patients (%)*	*Overall survival p value*	*Disease-free survival p value*
Gender			0.66	0.22
Male	70.5 (11.7)	46 (69.7)		
Female	70.2 (18.1)	20 (30.3)		
Overall	71.5 (13.8)	66 (100)		
Age, years			0.62	0.70
>70		36 (54.5)		
≤70		30 (45.5)		
Histological tumor location			0.01	0.98
Gastroesophageal junction		8 (12.1)		
Body		32 (48.5)		
Antrum		26 (39.4)		
pT *			<0.01	0.25
T1		11 (16.9)		
T2		8 (12.3)		
T3		19 (29.2)		
T4		27 (46.5)		
pN *			0.01	<0.01
N0		19 (29.2)		
N1		8 (12.3)		
N2		16 (24.6)		
N3		22 (33.8)		
Positive lymph node ratio*			<0.01	<0.01
Level of lymph node dissection*			0.02	0.20
D1		39 (60.0)		
D1+		18 (27.7)		
D2		8 (12.3)		
M*			0.01	0.24
M0		58 (87.9)		
M1		7 (12.1)		
Grade**			<0.01	0.47
1		2 (3.7)		
2		18 (32.7)		
3		35 (63.6)		
Stage*			<0.01	0.01
I		14 (21.5)		
II		13 (20.0)		
III		31 (47.7)		
IV		7 (10.8)		
Lauren classification***			0.07	0.81
Instestinal		27 (50.0)		
Diffuse		18 (33.3)		
Mixed		9 (16.7)		
Resection*			<0.01	0.88
R0		56 (86.2)		
R1		4 (6.2)		
R2		5 (7.7)		

* excluding 1 missing ** excluding 11 missing *** excluding 12 missing

lyzed using log-rank tests. P values < 0.05 were considered statistically significant.

Results

In the group of 66 patients with GC, men outnumbered women with a male/female ratio of 2.3:1. The mean patient age was 71.5±13.8 years (range 27-96).

The median follow-up period was 59.1 months with a total of 65198 person-days included in the study. At the end of follow-up, 4 patients were lost

(6.1%), 15 (22.7%) were alive and 47 died, indicating a disease-specific mortality of 71.2% and an overall median survival of 32.6 months. The median censorship interval was 29.6 months.

As far as the location of the tumors is concerned, 32 lesions were found at the body of the stomach, 26 at the antrum and 8 at the gastroesophageal junction (Siewert III). Consequently, 2 patients underwent central gastrectomy, 43 underwent subtotal gastrectomy, and 21 underwent total gastrectomy.

Histologically, all GCs were adenocarcinomas. Tumor TNM stage, grade, resection status, Lauren histological subtype and extent of lymph node dissection are shown in Table 1.

Survival rates were negatively correlated with pT at diagnosis (p<0.01), pN (p=0.01), positive lymph node ratio (p<0.01), M (p<0.01), TNM stage (p<0.01), grade (p<0.01) and the absence of R0 resection (p<0.01). DFS rates were affected by pN at diagnosis (p<0.01), positive lymph node ratio (p<0.01) and TNM stage (p= 0.01).

Immunohistochemistry data analysis

This study analyzed 63 surgical specimens; 3 specimens lacked immunohistochemical evaluation. Of those, 46 cases (73.0%) showed abnormal E-cadherin expression in IHC. The correlation of E-cadherin tissue expression with patient OS or DFS was not statistically significant, nor was it with gender, tumor T, N, grade, TNM stage, positive lymph node ratio or lymphovascular invasion (Table 2). However, there was a marginally decreased E-cadherin expression for the diffuse Lauren classification subtype (OR:0.72; p=0.09) and a tendency for increased expression with older age (OR:1.01; p=0.13), which did not reach statistical significance (Figure 1).

Table 2. Association of E-cadherin positivity (>30) with patient clinicopathological characteristics, overall survival and disease-free survival (n=83)

Characteristics	*p value*
Gender	1.00
Age > 70	0.13
pT	0.99
pN	0.99
Grade	0.80
Stage	0.27
Lauren classification	0.09
Positive lymph node ratio	0.50
Lymphovascular invasion	0.70
Overall survival	0.65
Disease-free survival	0.88

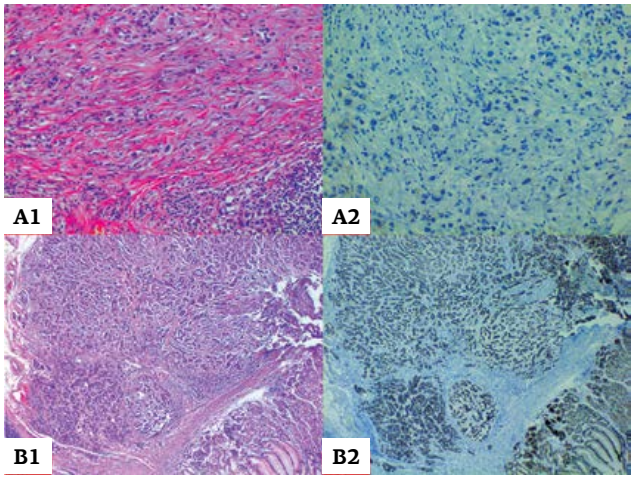

Figure 1. A1: H&E staining demonstrating diffuse type gastric carcinoma (x200); **A2:** Negative E-cadherin in gastric carcinoma tissue (x 200); **B1**: H&E staining in well differentiated intestinal type gastric carcinoma (x100); **B2**: positive E-cadherin expression in gastric carcinoma tissue (x100).

Discussion

E-cadherin is a transmembrane protein encoded by the CDH1 gene which is located on chromosome 16 (q 22.1) [4]. E-cadherin is a calcium-mediated membrane molecule which plays an important role in adhesion and differentiation of gastric epithelial cells, which is a very important protective mechanism against neoplasm transformation [5-7,11,12].

Generally, E-cadherin is highly expressed in well-differentiated cancers that maintain cell-cell adhesiveness and are less invasive while the expression of this molecule is reduced in poorly differentiated tumors that have lost their intercellular adhesion in parallel with the acquisition of high invasive potential [12,13]. In our study, 27% of the cases of GC showed negative E-cadherin expression in IHC. A similar study demonstrated a 38% rate of abnormal E-cadherin expression in IHC in GC patients [14].

This frequency among GC was reported to vary from 46 to 82% [13,15-17]. These differences may be related to the method of mutation assessment (E-cadherin expression by IHC or E-cadherin gene methylation or mutation). Low or absent E-cadherin expression is strongly involved in the pathogenesis of GC by several molecular mechanisms [11]. First, promoter hypermethylation is a mechanism of attenuating tumor suppressors and has been found to be significantly associated with decreased expression of E-cadherin in GC, es-

pecially in diffuse histological type [18]. Furthermore, somatic and germline mutations lead to low expression of E-cadherin in GC, especially also in diffuse histological type [19,20]. In addition, recent studies have shown that activation of E-cadherin transcriptional repressors, such as Snail and Slug [21], leads to downregulation of E-cadherin in GC [22,23]. Reduced or lost expression of a few microRNAs, including miR-200 family and miR-101, were also shown to inhibit E-cadherin expression through upregulating the expression of E-cadherin repressors [24,25]. Chan et al. [16] demonstrated that E-cadherin methylation was correlated with the depth of tumor invasion and nodal metastasis whereas Jawhari et al. [26] showed that E-cadherin mutation was associated with diffuse type cancer but not with tumor grade or stage. These molecular mechanisms result in the low-expression and dysfunction of E-cadherin, which further leads to development and progression of GC.

Analyzing the results of E-cadherin expression, we found positive immunoreactivity in 73% of GC, mainly iin ntestinal-type tumors (80.8%) compared with only 50% of the diffuse type tumors. Similarly, Czyzewska et al. [14] found positive immunoreactivity in 65% of GC, mainly in intestinal-type tumors (69.38%) compared with only 45% of the diffuse type tumors. They have also noted the negative staining in the remaining 30.61% of intestinal type carcinomas (all poorly differentiated tumors) and 54.54% of the diffuse type carcinomas [14]. In agreement with these results, similar studies reported variable decrease (between 17 and 92%) of E-cadherin expression in GC (compared with normal non-neoplastic gastric mucosa), mainly for poorly differentiated intestinal-type tumors and diffuse type carcinomas [6,27-30].

Literature stands equivocal about the association between E-cadherin expression, histopathology and tumor invasiveness. Our results showed that there was no statistically significant correlation between E-cadherin expression and tumor invasiveness (tumor grade, stage or regional lymph node involvement). On the other hand, Anbiaee et al. [31] showed a significant correlation between abnormal E-cadherin expression and high grade tumors, as well as with the number of regional lymph node involvement. In the same frame, Karayiannakis et al. [32] found a significant correlation of E-cadherin expression with tumor differentiation grade, location and lymph node involvement. Also Ohno et al. [33] reported that tumors with "abnormal" E-cadherin expression positively correlated with venous invasion and lymph node metastasis. However, other researchers described lack of correlation between the E-cadherin expression and lymph node involvement [15]. No correlation was also found between E-cadherin expression and the lymphatic pathway of invasion or lymph node metastasis [27]. Finally, a recent study was confirmatory to our results, demonstrating that high E-cadherin expression was more frequently found in GC of intestinal type and well differentiated while poorly differentiated tumors and diffuse type carcinomas demonstrated a high rate of negative reactivity [13].

The striking finding of our study was that the expression of E-cadherin was not correlated with DFS. This finding is of interest since a recent meta-analysis revealed that reduced E-cadherin expression was significantly correlated with poor OS in GC patients [34]. Moreover, negativity of E-cadherin was significantly associated with TNM stage, the depth of invasion, lymph node metastasis, distant metastasis, grade of differentiation, vascular invasion and histological type of GC [34]. In the same frame were the results of another meta-analysis where a strong link was found between the reduced E-cadherin expression and poor 5-year OS [3]. In that study, the depth of invasion, lymph node spread, presence of distant metastasis and TNM stage seemed to demonstrate a significant prognostic role [3].

These results, though, should be approached with caution since the majority of the patients involved in these meta-analyses were of Asian origin. Moreover, there are diversities and discrepancies among studies since some of them evaluated E-cadherin methylation, others E-cadherin gene mutations and the rest evaluated E-cadherin HIC expression. The latter subcategory is even more diverse since there are many immunochemistry models published in the literature evaluating E-cadherin expression. New trials and meta-analyses in patients of European origin would be more helpful in evaluating the prognostic value of the results of studies such as ours.

Conclusions

In the current study, 73.0% of the evaluated tumors showed abnormal E-cadherin expression in IHC but the correlation of E-cadherin tissue expression with patient OS or DFS was not statistically significant, as well as with gender, tumor T, N, grade, TNM stage, positive lymph node ratio or lymphovascular invasion. Literature stands equivocal about the association between E-cadherin mutation, histopathology and tumor inva-

siveness. Our results further strengthen the need of larger studies to fully elucidate the predictive role of E-cadherin in the natural history of GC.

Acknowledgements

We thank Prof. Kitty Pavlakis for her contribution to the preparation and analysis of the histological data of the current study.

Author contributions

Schizas D, Machairas A and Liakakos T designed the study; Schizas D, Moris D, Kanavidis P and Michalinos A collected the patient's clinical data; Schizas D, Moris D Oikonomou D and Kanavidis P analyzed the data and wrote the paper; and Liakakos T and Machairas A supervised the manuscript.

Conflict of interests

The authors declare no confict of interests.

References

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010;127:2893-2917.
2. Chaffer CL, Weinberg RA. A perspective on cancer cell metastasis. Science 2011;331:1559-1564.
3. Li T, Chen J, Liu QL, Huo ZH, Wang ZW. Meta-analysis: E-cadherin immunoexpression as a potential prognosis biomarker related to gastric cancer metastasis in Asian patients. Eur Rev Med Pharmacol Sci 2014;18:2693-2703.
4. Takeichi M. Cadherins: a molecular family important in selective cell-cell adhesion. Annu Rev Biochem 1990;59:237-252.
5. Takeichi M. Cadherins in cancer: implications for invasion and metastasis. Curr Opin Cell Biol 1993;5:806-811.
6. Chan AO. E-cadherin in gastric cancer. World J Gastroenterol 2006;12:199-203.
7. Liu X, Chu KM. E-cadherin and gastric cancer: cause, consequence, and applications. BioMed Res Int. 2014;2014:637308.
8. Huang L, Xu AM, Liu S, Liu W, Li TJ. Cancer-associated fibroblasts in digestive tumors. World J Gastroenterol 2014;20:17804-17818.
9. Oka H, Shiozaki H, Kobayasi K et al. [Immunoreactive expression of E-cadherin in human gastric cancer: preliminary report]. Nihon Geka Gakkai zasshi 1990;91:1814.
10. Yong CS, Ou Yang CM, Chou YH, Liao CS, Lee CW, Lee CC. CD44/CD24 expression in recurrent gastric cancer: a retrospective analysis. BMC Gastroenterol 2012;12:95.
11. Jeanes A, Gottardi CJ, Yap AS. Cadherins and cancer: how does cadherin dysfunction promote tumor progression? Oncogene 2008;27:6920-6929.
12. Birchmeier W, Behrens J. Cadherin expression in carcinomas: role in the formation of cell junctions and the prevention of invasiveness. Biochimica Biophysica Acta 1994;1198:11-26.
13. Stanculescu D, Margaritescu C, Stepan A, Mitrut AO. E-cadherin in gastric carcinomas related to histological prognostic parameters. Romanian J Morphol Embryol 2011;52(3 Suppl):1107-1112.
14. Czyzewska J, Guzinska-Ustymowicz K, Ustymowicz M, Pryczynicz A, Kemona A. The expression of E-cadherin-catenin complex in patients with advanced gastric cancer: role in formation of metastasis. Folia Histochemica Cytobiologica 2010;48:37-45.
15. Zhou YN, Xu CP, Han B et al. Expression of E-cadherin and beta-catenin in gastric carcinoma and its correlation with the clinicopathological features and patient survival. World J Gastroenterol 2002;8:987-993.
16. Chan AO, Lam SK, Wong BC et al. Promoter methylation of E-cadherin gene in gastric mucosa associated with Helicobacter pylori infection and in gastric cancer. Gut 2003;52:502-506.
17. Guzman P, Araya J, Villaseca M et al. [Immunohistochemical expression of the E-cadherin-catenin complex in gastric cancer]. Revista Medica de Chile 2006;134:1002-1009.
18. Graziano F, Arduini F, Ruzzo A et al. Combined analysis of E-cadherin gene (CDH1) promoter hypermethylation and E-cadherin protein expression in patients with gastric cancer: implications for treatment with demethylating drugs. Ann Oncol 2004;15:489-492.
19. Berx G, Becker KF, Hofler H, van Roy F. Mutations of the human E-cadherin (CDH1) gene. Hum Mutation 1998;12:226-237.
20. Brooks-Wilson AR, Kaurah P, Suriano G et al. Germline E-cadherin mutations in hereditary diffuse gastric cancer: assessment of 42 new families and review of genetic screening criteria. J Med Genet 2004;41:508-517.
21. Uchikado Y, Okumura H, Ishigami S et al. Increased Slug and decreased E-cadherin expression is related to poor prognosis in patients with gastric cancer. Gastric Cancer 2011;14:41-49.
22. Becker KF, Rosivatz E, Blechschmidt K, Kremmer E, Sarbia M, Hofler H. Analysis of the E-cadherin repressor Snail in primary human cancers. Cells Tissues Organs 2007;185:204-212.
23. Alves CC, Carneiro F, Hoefler H, Becker KF. Role of the epithelial-mesenchymal transition regulator

Slug in primary human cancers. Frontiers Biosci 2009;14:3035-3050.

24. Carvalho J, van Grieken NC, Pereira PM et al. Lack of microRNA-101 causes E-cadherin functional deregulation through EZH2 up-regulation in intestinal gastric cancer. J Pathol 2012;228:31-44.
25. Kurashige J, Kamohara H, Watanabe M et al. MicroRNA-200b regulates cell proliferation, invasion, and migration by directly targeting ZEB2 in gastric carcinoma. Ann Surg Oncol 2012;19 (Suppl 3):S656-664.
26. Jawhari A, Jordan S, Poole S, Browne P, Pignatelli M, Farthing MJ. Abnormal immunoreactivity of the E-cadherin-catenin complex in gastric carcinoma: relationship with patient survival. Gastroenterology 1997;112:46-54.
27. Mayer B, Johnson JP, Leitl F et al. E-cadherin expression in primary and metastatic gastric cancer: down-regulation correlates with cellular dedifferentiation and glandular disintegration. Cancer Res 1993;53:1690-1695.
28. Shimoyama Y, Hirohashi S. Expression of E- and P-cadherin in gastric carcinomas. Cancer Res 1991;51:2185-2192.
29. Zhang HK, Zhang QM, Zhao TH, Li YY, Yi YF. Expression of mucins and E-cadherin in gastric carcinoma and their clinical significance. World J Gastroenterol 2004;10:3044-3047.
30. Chen HC, Chu RY, Hsu PN et al. Loss of E-cadherin expression correlates with poor differentiation and invasion into adjacent organs in gastric adenocarcinomas. Cancer Lett 2003;201:97-106.
31. Anbiaee R, Mojir Sheibani K, Torbati P, Jaam H. Abnormal expression of e-cadherin in gastric adenocarcinoma, and its correlation with tumor histopathology and helicobacter pylori infection. Iranian Red Crescent Med J 2013;15:218-222.
32. Karayiannakis AJ, Syrigos KN, Chatzigianni E, Papanikolaou S, Karatzas G. E-cadherin expression as a differentiation marker in gastric cancer. Hepatogastroenterology 1998;45:2437-2442.
33. Ohno T, Aihara R, Kamiyama Y, Mochiki E, Asao T, Kuwano H. Prognostic significance of combined expression of MUC1 and adhesion molecules in advanced gastric cancer. Eur J Cancer 2006;42:256-263.
34. Xing X, Tang YB, Yuan G et al. The prognostic value of E-cadherin in gastric cancer: a meta-analysis. Int J Cancer 2013;132:2589-2596.