Original Article

Predictive value of E-cadherin and EpCAM for detection of metastatic lymph node in early gastric cancer

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Abstract

Objective: There has been a demand for a tumor-specific marker for metastatic lymph nodes in sentinel navigation surgery for gastric cancer. The aim of this study is to analyze protein expression in both primary tumors and metastatic lymph nodes in early gastric cancer patients.

Methods: We collected primary tumors and metastatic lymph nodes from 71 patients who underwent curative gastrectomy and pathologically diagnosed with T1N1 or T1N2 (8th Union for International Cancer Control 8th edition/American Joint Committee on Cancer staging system) gastric cancer. Immunohistochemistry was used to determine the expression of six cell membrane proteins, including carcinoembryonic antigen (CEA), E-cadherin, epithelial cell adhesion molecule (EpCAM), P-cadherin, CD44v6, and c-erbB2 in the patient samples.

Results: The expression of CEA, E-cadherin, EpCAM, P-cadherin, CD44v6 and c-erbB2 in the evaluable primary tumor samples was 75.4%, 97.1%, 100%, 89.9%, 11.1% and 7.2%, respectively. Among cases wherein both the primary tumor and metastatic lymph nodes were evaluable, double positivity (expression in both primary tumor and metastatic lymph nodes) was observed for CEA, E-cadherin, EpCAM, P-cadherin, CD44v6 and c-erbB2 in 53.2%, 97.9%, 98.1%, 76.6%, 0 and 6.8% of the cases, respectively. The proportion of metastatic lymph nodes positive for CEA, E-cadherin, EpCAM, P-cadherin, CD44v6 and c-erbB2 was 71.4%, 100%, 98.1%, 83.7%, 0, and 75%, respectively in primary tumors positive for the same markers.

Conclusions: E-cadherin and EpCAM had an overlap of 100% and 98.1% between the primary tumor and metastatic lymph nodes, respectively. Thus, E-cadherin and EpCAM are potential molecular markers to detect metastatic lymph nodes in patients with early gastric cancer.

Keywords: Gastric cancer; tumor-associated protein; E-cadherin; EpCAM; lymph node

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Introduction

The strategy for treating patients with gastric cancer depends on the extent of lymph node metastasis. Radical gastrectomy with lymph node dissection is usually performed for localized advanced gastric cancer. Limited resection, including endoscopic submucosal dissection and function-preserving gastrectomy, is effective for tumors with a low risk of lymph node metastasis (1,2). Sentinel navigation surgery can also be tried to reduce surgical extent and various limited resections such as endoscopic full-thickness resection, wedge resection, and segmental resection could be applied, when no metastatic lymph node was confirmed by evaluation of sentinel lymph nodes (3,4).

Preoperative assessment of metastasis to the lymph node in gastric cancer patients is limited. Conventionally, computed tomography (CT) is used to assess the lymph node. However, only 60%–70% cases of lymph node

staging by CT are accurate. Attempts to improve this efficiency by performing positron emission tomography (PET) have been proved futile owing to low sensitivity (5-7). Several tracers, such as indocyanine green, isosulfan blue, and radioactive colloid, have been used while detecting the sentinel node (8). However, these tracers are not tumor-specific and only show the lymphatic channels between the primary tumor and adjacent lymph nodes. Multiple sentinel basins are detected in some cases, and intraoperative frozen examination must be conducted to confirm the metastatic nature of the sentinel node. Thus, there has been a demand for a tumor-specific marker to identify metastatic lymph nodes in sentinel navigation surgery. The tumor-specific marker would facilitate minimal dissection of sentinel basin and surgical extent for patients with gastric cancer.

In this study, we aim to identify the molecular markers expressed in primary and paired metastatic lymph nodes. Expression of a membrane molecule in the primary tumor and paired metastatic lymph nodes that is detectable intraoperatively is a tumor-specific marker for metastatic lymph nodes. Thus, we evaluated the expression of candidates in both primary and paired lymph nodes to identify potential tumor-specific targets for sentinel lymph node navigation surgery

Materials and methods

Patients and tissues

Medical records were reviewed for 2,246 gastric adenocarcinoma patients who underwent gastrectomy between July 2001 and December 2005 at the National Cancer Center. Among these, we included patients who met the following conditions. First, patients who were pathologically diagnosed as T1N1M0 or T1N2M0 (Union for International Cancer Control 8th edition) (9); second, patients who underwent total or subtotal gastrectomy with lymphadenectomy. The exclusion criteria are patients who received neoadjuvant chemotherapy. Through this screening process, a total of 71 patients' data were analyzed.

Patients' demographic and pathological parameters, such as age, sex, tumor location, tumor size, histological type, and Lauren and tumor-node-metastasis (TNM) classification, were evaluated. Histological types were classified according to the World Health Organization and Lauren's classification (10,11). Tumors sized at 0.2–2.0 mm and >2.0 mm was defined as micrometastasis and macrometastasis, respectively. All the pathological analyses were performed by a single pathologist specialized in gastric cancer (M.C.K.).

In descriptive statistics, continuous variables were shown as $\bar{x}\pm s$ and categorical variables were presented as proportions. This study was approved by the Institutional Review Board at the National Cancer Center (Approval No. NCCNCS-09-231) and was compliant with the principles embodied in the Declaration of Helsinki. The requirement for written informed consent was waived for this study due to no risk of disclosure of personal identifiable information and no harm to patients.

Tissue microarray (TMA)

We designed a TMA to analyze the protein expression in the primary tumors (12). Formalin-fixed paraffinized samples from 71 patients were collected from the archives of the Department of Pathology, National Cancer Center, Korea. Representative areas in each tumor were identified based on the hematoxylin and eosin stained slides. Core tissue biopsies (2 mm in diameter) were performed on each donor tissue block and arranged in new recipient paraffin tissue blocks using a trephine apparatus (Superbiochips Laboratories, Seoul, Republic of Korea). The most representative metastatic node of each patient sample was used to stain the lymph nodes.

Immunohistochemistry

Based on the literature, we selected six candidate cell membrane molecules, including the carcinoembryonic antigen (CEA), E-cadherin, epithelial cell adhesion molecule (EpCAM), P-cadherin, CD44v6, and c-erbB2. They are strongly correlated with lymph node metastasis or significantly expressed in both primary tumor and metastatic lymph nodes of gastric cancer patients (13-21). We performed immunohistochemistry for all the candidates in both tumor sites. Automated staining was performed by BenchMark XT (Ventana).

For immunohistochemistry, 4 μm-thick sections were made from the TMA block. Sections were deparaffinized, rehydrated, and incubated in 3% hydrogen peroxide for 10 min to block endogenous peroxidase activity. The antigens were retrieved using heat (95 °C) for 30 min in pH 8.0 Tri-EDTA buffer (CC1, Ventana). Slides were immersed in 3% (v/v) hydrogen peroxide for 4 min at 37 °C to block endogenous peroxidase activity. Subsequently, the slides

were washed and incubated with primary antibodies for 32 min at 42 °C. The antibodies used were anti-CEA (mouse monoclonal; 0.2 μg/mL; M7072, DAKO Corp., Carpinteria, CA), anti-E-cadherin (mouse monoclonal; 1 μg/mL; 610182, BD Transduction Laboratories, San Jose, CA), anti-EpCAM (mouse monoclonal; 0.5 μg/mL; OP187, Calbiochem, Darmstadt, Germany), anti-P-cadherin (mouse monoclonal; 1 μg/mL; 610228, BD Transduction Laboratories, San Jose, CA), anti-CD44v6 (mouse monoclonal; 0.25 μg/mL; VFF-7 clone; Novocastra, Benton Lane, Newcastle, UK), and anti-c-erbB2 (rabbit polyclonal; 5 μg/mL; AB8054, DAKO Corp., Carpinteria, CA). The sections were then incubated with horseradish peroxidase-conjugated secondary antibodies (ultraView Universal DAB detection kit, Ventana) for 8 min at room temperature and stained using the ultraView universal DAB kit (Ventana) for 8 min followed by hematoxylin counterstaining.

Analysis of tissue samples

Only cell membrane staining was used to determine positivity and any cytoplasmic staining was neglected. The abundance of tumor-positive cells was categorized as: ≤ 10%, 0; >10% but ≤50%, 1+; >50%, 2+ for CEA, E-cadherin, EpCAM, P-cadherin, and CD44v6. The 1+ and 2+ cases were designated as positive and cases of 0 were designated as negative. In some studies, samples are considered negative for E-cadherin, if the staining intensity decreases in the cancer tissue than in normal epithelial cell. However, in this study, we considered it positive since it is still detectable by the antibody. We followed the consensus panel recommendations for HER2 scoring of gastric cancers and c-erbB2 staining was classified as 0, 1+, 2+, or 3+ (22). The 2+ and 3+ cases were considered positive in this study.

Results

Clinicopathological characteristics

Table 1 shows patients' demographic and pathological data. The mean age of patients was 58.8±11.5 years; the patient cohort comprised 66.2% of male patients. The most common location for the tumor was the lower one-third of the stomach (70.4%) and 63.4% of the tumors were intestinal type. The majority of patients (87.3%) had tumors that invaded the submucosal layers and 66.2% of patients had one metastatic lymph node.

Table 1 Clinicopathological characteristics (N=71)

Characteristics	n (%)
Age ($\bar{x}\pm s$) (year)	58.8±11.5
Sex	
Male	47 (66.2)
Female	24 (33.8)
Tumor location	
Lower	50 (70.4)
Middle	16 (22.5)
Upper	5 (7.0)
Tumor size ($\bar{x}\pm s$) (cm)	4.7±2.5
Histological type	
WD	14 (19.7)
MD	27 (38.0)
PD	21 (29.6)
SRC	8 (11.3)
Mucinous	1 (1.4)
Lauren's classification	
Intestinal	45 (63.4)
Diffuse/mixed	23 (32.4)
Indeterminate	3 (4.2)
Depth of invasion	
Mucosa	9 (12.7)
Submucosa	62 (87.3)
Number of metastatic lymph nodes	
1	47 (66.2)
2	20 (28.2)
3–6	4 (5.6)

WD, well differentiated; MD, moderately differentiated; PD, poorly differentiated; SRC, signet ring cell.

Expression of molecular markers in primary tumor and metastatic lymph nodes

The expression of CEA, E-cadherin, EpCAM, P-cadherin, CD44v6, and c-erbB2 in the primary tumor tissue, excluding the non-applicable cases, was 75.4% (52/69), 97.1% (67/69), 100% (65/65), 89.9% (62/69), 11.1% (7/63) and 7.2% (5/69), respectively. The expression of CEA, E-cadherin, EpCAM, P-cadherin, CD44v6, and c-erbB2 in the metastatic lymph nodes was 69.4% (34/49), 98.0% (48/49), 98.4% (61/62), 83.7% (41/49), 0 (0/47), and 13.0% (6/46) respectively (*Table 2*). *Figure 1* show representative immunostainings of the six molecular markers in metastatic lymph nodes.

Table 2 Expressions of six molecular markers in primary (T) and metastatic lymph nodes (N)

Markers	n (%)	
	Primary tumor	Metastatic lymph nodes
CEA		
Positive	52 (75.4)	34 (69.4)
Negative	17 (24.6)	15 (30.6)
NA	2	22
E-cadherin		
Positive	67 (97.1)	48 (98.0)
Negative	2 (2.9)	1 (2.0)
NA	2	22
EpCAM		
Positive	65 (100)	61 (98.4)
Negative	0 (0)	1 (1.6)
NA	6	9
P-cadherin		
Positive	62 (89.9)	41 (83.7)
Negative	7 (10.1)	8 (16.3)
NA	2	22
CD44v6		
Positive	7 (11.1)	0 (0)
Negative	56 (89.9)	47 (100)
NA	8	24
c-erbB2		
Positive	5 (7.2)	6 (13.0)
Negative	64 (92.8)	40 (87.0)
NA	2	25

CEA, carcinoembryonic antigen; EpCAM, epithelial cell adhesion molecule; NA, non-applicable.

Correspondence between primary tumor and metastatic lymph nodes

Among patients for whom both the primary tumor and metastatic lymph nodes were evaluable, 53.2% (25/47) of samples expressed CEA expression in both the sites of cancer [T(+)N(+)]. The double positivity of E-cadherin, EpCAM, P-cadherin, CD44v6, and c-erbB2 was observed in 97.9% (46/47), 98.1% (51/52), 76.6% (36/47), 0 (0/43) and 6.8% (3/44), respectively. The proportion of metastatic lymph nodes positive for CEA, E-cadherin, EpCAM, P-cadherin, CD44v6, and c-erbB2 were 71.4% (23/35), 100% (46/46), 98.1% (51/52), 83.7% (36/43), 0 (0/5), and 75.0% (3/4) , respectively in the primary tumor positive for the same markers [N(+)/T(+)] (*Table 3*).

Discussion

In this study, we determined the expression of six cell membrane molecules in primary tumor and paired metastatic lymph nodes in patients with early gastric cancer. Each molecular marker was expressed to different extents in the primary tumors. E-cadherin and EpCAM were expressed the most in both primary tumors and metastatic lymph nodes (ranging between 97.1% and 100%). Moreover, the rate of concordance (T+N+ or T−N−) was 100% and 98.1% for E-cadherin and EpCAM, respectively; there was only one discordant case (T+N−) for EpCAM. Thus, E-cadherin and EpCAM might be cancer-specific markers that can be used to analyze the sentinel node for patients with early gastric cancer.

Accurately evaluating the status of metastasis in the lymph node(s) is crucial in early gastric cancer to help determine the need for limited resection in patients. Numerous molecular markers have been investigated to predict lymph node metastasis in gastric cancer till date. However, most of these studies have used advanced gastric cancer tissues with very few experiments on early gastric cancer tissues (23-26). Moreover, these molecular markers have usually been characterized only in primary tumors and not in metastatic lymph nodes. There are only a few reports on the increased expression of markers in metastatic lymph nodes and its correlation with prognosis of gastric cancer and/or treatment (20,27-29). The concordance of molecular markers between primary tumors and metastatic lymph nodes remains to be investigated. This study aims at identifying the candidates that can be used as cancer-specific markers to determine the need for limited resection and examine both primary tumors and paired metastatic lymph nodes in early gastric cancer patients.

We used six candidate molecular markers (CEA, E-cadherin, EpCAM, P-cadherin, CD44v6, and c-erbB2) for this study. CEA is an important tumor marker in multiple types of cancers. Several studies have shown that CEA staining significantly correlates with lymph node metastasis in gastric cancer (13). E-cadherin and P-cadherin are transmembrane glycoproteins localized in the adherent junctions of epithelial cells (14). The membrane staining of E-cadherin correlates with lymph node metastasis (15,16,30). EpCAM is also a transmembrane glycoprotein that mediates Ca^{2+}-independent homotypic cell-cell adhesion (31). The levels of EpCAM increase in gastric cancer tissue and metastatic lesions, indicating that it is a promising therapeutic target (32). CD44v6 is an isoform of

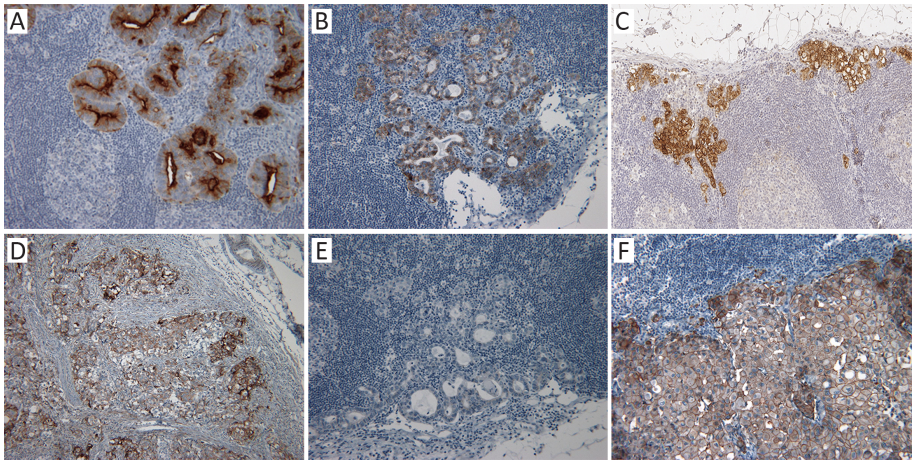

Figure 1 Immunohistochemistry for expression of (A) CEA; (B) E-cadherin; (C) EpCAM; (D) P-cadherin; (E) CD44v6 and (F) c-erbB2 in metastatic lymph nodes (there was no positive cases for CD44v6). CEA, carcinoembryonic antigen; EpCAM, epithelial cell adhesion molecule.

Table 3 Correspondence of six molecular markers between primary tumor (T) and metastatic lymph nodes (N) in evaluable cases of lymph node metastasis

Markers	Cases	n (%)				n/N (%)*
		T(+)N(+)	T(+)N(−)	T(−)N(+)	T(−)N(−)	N(+)/T(+)
CEA	47	25 (53.2)	10 (21.3)	7 (14.9)	5 (10.6)	25/35 (71.4)
E-cadherin	47	46 (97.9)	0 (0)	0 (0)	1 (2.1)	46/46 (100)
EpCAM	52	51 (98.1)	1 (1.9)	0 (0)	0 (0)	51/52 (98.1)
P-cadherin	47	36 (76.6)	7 (14.9)	3 (6.4)	1 (2.1)	36/43 (83.7)
CD44v6	43	0 (0)	5 (11.6)	0 (0)	38 (88.4)	0/5 (0)
c-erbB2	44	3 (6.8)	1 (2.3)	3 (6.8)	37 (84.1)	3/4 (75.0)

CEA, carcinoembryonic antigen; EpCAM, epithelial cell adhesion molecule; *, the proportion of metastatic lymph nodes positive in the primary tumors positive.

CD44 which is a glycosylated transmembrane protein expressed in a variety of epithelial and mesenchymal cells as well as tumor cells (33). CD44v6 correlates with lymph node metastasis even in early gastric cancer (17-19). Our sixth marker, c-erbB2 is crucial for the pathogenesis and progression of several tumors and an important prognostic marker for gastric cancer, suggesting a survival benefit for gastric cancer patients undergoing anti-HER2 therapy (34,35). Previous studies have reported high levels of c-erbB2 in primary tumors and their corresponding metastatic lymph nodes (20,21,27).

Among the six markers, E-cadherin and EpCAM exhibited the highest positive rates (97.1% and 100%, respectively) in the primary tumor samples and concordance (100% and 98.1%, respectively) between primary tumors and metastatic lymph nodes. This suggests that most cases of early gastric cancer with lymph node metastasis express E-cadherin and EpCAM in the primary tumor and metastatic lymph nodes. Injecting E-cadherin or EpCAM around the primary tumor will also enable fluorescence mediated visualization of the metastatic lymph nodes. Limited resection may be performed based on the presence of E-cadherin or EpCAM in the lymph node(s) in the future.

However, this study has several limitations. We only selected six molecules among a plethora of molecular markers that correlate with lymph node metastasis in gastric cancer. Moreover, this study was performed using 71 patient samples from a single center in Korea, thus, there might be some selection biases in this cohort. Furthermore, a significant number of metastatic lymph nodes could not be analyzed owing to the small size of metastatic tumors that could not be embedded in the section used for immunohistochemistry. Finally, this study

does not include any tests for the validation of the findings. Therefore, further experiments need to be conducted in the future using other molecules involved in early gastric cancer in the primary tumors with paired metastatic lymph nodes in a larger cohort. Furthermore, examinations using independent gastric cancer tissue samples need to be tested to confirm the findings of this study.

Conclusions

Taken together, our findings show that E-cadherin and EpCAM exhibit high rates of expression in primary tumors and concordance between primary tumor and metastatic lymph nodes in patients with early gastric cancer. Thus, E-cadherin and EpCAM are potential molecular markers that could be used to identify metastatic lymph nodes in patients with early gastric cancer.

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Footnote

Conflicts of Interest: These authors have no conflicts of interest to declare.

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