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Original Article

Expression and clinical significance of E-cadherin and survivin in primary and metastatic lymph nodes of advanced gastric carcinoma

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Abstract: Objective: Retrospective analysis: This study aimed to assess the expression and clinical relevance of E-cadherin and Survivin in primary and metastatic lymph nodes of advanced gastric carcinoma. Methods: A total of 47 cases of primary and metastatic lymph nodes in advanced gastric carcinoma were examined, and the expressions of e-cadherin and survivin were assessed using immunohistochemistry. We examined the disparities in e-cadherin and survivin expression between primary lesions and their metastases. Results: Among 47 cases, a highly positive expression of e-cadherin was observed in 14 cases, while survivin expression was down-regulated in 15 cases. This was more frequently associated with well-differentiated carcinoma than with poorly differentiated carcinoma. The three-year survival rate correlated with elevated e-cadherin expression in metastatic lymph nodes of advanced gastric carcinoma. Conclusions: Re-expression of E-cadherin is observed in tumor cells of certain metastatic lymph nodes, predominantly in those with low malignancy. E-cadherin facilitates the adhesion of tumor cells, potentially resulting in focal aggregation, which can subsequently proliferate at specific sites to form metastases, particularly in instances of high differentiation. In comparison to the primary tumors, Survivin expression in tumor cells of certain metastatic lymph nodes is diminished, particularly in tumor cells exhibiting low malignancy. However, it does not inherently signify the attenuation of malignant proliferation. The downregulation of Survivin expression shows no significant correlation with the 3-year survival rate of patients. E-cadherin and Survivin contribute to the composition of the tumor microenvironment. In metastatic lymph nodes, the re-expression of E-cadherin in certain tumor cells may facilitate the down-regulation of Survivin expression. The tumor microenvironment consists of various factors that interact with one another. Concomitant medication may enhance therapeutic efficacy. The 3-year survival rate of patients with metastatic lymph nodes is associated with the re-expression of E-cadherin in advanced gastric cancer. E-cadherin serves as an independent prognostic indicator for advanced gastric cancer.

Keywords: Advanced gastric carcinoma, primary lesion, metastasis, survivin, E-cadherin

Introduction

The invasion and metastasis of tumor cells are essential biological processes in the advancement of malignant tumors. These processes involve various mechanisms, such as tumor cell adhesion, migration, proliferation, extracellular matrix degradation, immune evasion, and tumor angiogenesis. Due to their pivotal role in cancer progression, significant focus has been directed towards elucidating the biomolecular mechanisms that govern tumor initiation and metastasis to enhance patient prognosis.

E-cadherin is a crucial adhesion molecule that facilitates cell-cell interactions. The loss or abnormal expression of E-cadherin can result in structural and functional alterations among cells, diminishing cell-cell adhesion and promoting the detachment of cancer cells from the primary tumor. This separation allows cancer cells to infiltrate adjacent tissues and metastasize through lymphatic and blood vessels or by direct implantation. Survivin, a constituent of the inhibitor of apoptosis protein (IAP) family, is essential in inhibiting apoptosis. While it is expressed at low levels in most normal tissues,

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it is significantly overexpressed in nearly all malignant tumors. The anomalous expression of E-cadherin has been demonstrated to activate the Wnt signaling pathway, with survivin regarded as a downstream effector of this pathway.

The multifactorial etiology and diverse clinicopathological features of malignancies significantly influence their aggressive biological behavior [1, 2]. Multiple studies have underscored the crucial functions of E-cadherin in cellular adhesion and survivin in malignant proliferation.

In gastric carcinoma, numerous studies have shown that E-cadherin immunoexpression is significantly associated with tumor grade and stage, making it a valuable prognostic marker. Evidence indicates that tumor progression is not merely due to unchecked cell proliferation, but also entails a decrease in apoptosis [3, 4]. Survivin, a multifunctional protein, modulates cell division, suppresses apoptosis, and promotes angiogenesis. The considerable variability in survivin expression levels among malignant tumors renders its prognostic significance a matter of continued contention. The main aim of this study was to examine the expression and clinical relevance of E-cadherin and survivin in 47 instances of primary gastric carcinoma and metastatic lymph nodes.

Material and methods

Tissue samples

Retrospective Study: The study encompassed 47 cases of primary and metastatic lymph nodes from patients admitted to the Department of General Surgery at The Second Hospital of Hebei Medical University over a three-year period (2015-2018), all diagnosed in the Department of Pathology of the hospital. The inclusion criteria mandated that participants satisfied the following conditions at enrollment: (1) a minimum age of 18 years, (2) no previous record of preoperative neoadjuvant chemoradiotherapy or immunotherapy, (3) exclusion of patients with other malignant tumors, and (4) surgical procedures conducted at our hospital. The exclusion criteria included individuals who (1) did not undergo surgery, (2) received preoperative chemoradiotherapy and immunotherapy, (3) succumbed to other diseases, or (4) could not be monitored post-surgery.

The biological specimens consisted of surgical samples of primary and metastatic lymph nodes, preserved in 10% neutral buffered formalin, processed through the conventional paraffin embedding technique, and stained using Hematoxylin-Eosin (HE).

This study comprised 39 men and 8 women. The age distribution varied from 39 to 78 years, with an average age of 60.3 years. There were 27 instances of low-differentiated adenocarcinoma and 20 instances of highly differentiated adenocarcinoma. There were 32 cases with a primary tumor diameter exceeding 5 cm and 15 cases with a primary tumor diameter less than 5 cm. In 39 cases, the entire gastric wall was invaded, while in 8 cases it was not invaded.

Immunohistochemical staining

Following sectioning, dewaxing, and antigen retrieval, apply drops of an endogenous peroxidase blocker, followed by 5% goat serum to seal the tissue. Dilute the primary antibody solutions of E-cadherin and Survivin at a ratio of 1:150, then add the appropriate volume of primary antibody. Subsequently, apply drops of a biotin-labeled secondary antibody, followed by drops of horseradish peroxidase-labeled streptavidin. Perform DAB color development, followed by Hematoxylin staining, and proceed with gradient alcohol dehydration (75% I, 85% II, 95% III, 100% IV for 6 minutes each). Dehydration, sealing procedure. Mouse anti-human monoclonal E-cadherin antibody and mouse anti-human monoclonal Survivin antibody were acquired from Zhengneng Company, while the mouse SP immunohistochemical staining kit, DAB color development kit, and antigen retrieval solution were obtained from Beijing Zhongshan Jinqiao Reagent Company. In this experiment, adjacent normal gastric mucosal cells served as the control group.

Main instruments: HM 355s paraffin microtome Thermo Fisher, USA; E0988 embedding machine biyuntian, domestic; E0990 tissue spreader biyuntian, domestic; Hlr-198f refrigerator Haier, domestic; Hh-w21-600 electric thermostatic water bath box Shanghai Botai, domestic; Ms204 electronic balance METTLER TOLEDO Switzerland; Micropipette Gilson, France; BX51 electron microscope Olympus, Japan.

E-cadherin is prevalent in the junctions of epithelial cell membranes. The stable connection

Table 1. Relationship between E-cadherin expression and different histopathological features in primary lesions of advanced gastric carcinoma

Variant	N	E-cadherin		P
		-	+	
Gender				
Male	39	36	3	
Female	8	7	1	>0.05
Age				
<60	18	15	3	
≥60	29	28	1	>0.05
Differentiated degree				
Poor differentiation	27	27	0	
Medium-high differentiation	20	16	4	<0.05
Depth of invasion				
Not Full-thickness	8	7	1	
Full-thickness	39	36	3	>0.05
size				
<5 CM	32	31	1	
≥5 CM	15	12	3	>0.05

between E-cadherin and neighboring cells is established through the formation of a complex with catenin protein, which is subsequently anchored to the cytoskeleton. E-cadherin's function in epithelial cells is to preserve their adhesive properties and support the maintenance of morphological and structural integrity.

E-cadherin is localized on the cell membrane, exhibiting continuous staining in normal cells, and demonstrates positive expression in the presence of yellow particles. The classification based on the percentage of positive cells is as follows: grade 1 for 0% to 50%, grade 2 for 51% to 80%, and grade 3 for 81% to 100%. In the primary tissue section, a positive expression was designated when the percentage of positive cells ranged from 81-100%, corresponding to grade 3 staining, which was considered normal. Conversely, when the percentage of positive cells fell below 80%, grade 1 and 2 staining were classified as negative expressions. In metastatic lymph node tissue sections, a staining rating that exceeds that of the primary site indicates a positive reexpression in the metastatic lymph node.

Survivin can directly or indirectly suppress apoptotic signals and promote apoptosis by inhibiting the activity of cysteine-containing aspartate proteolytic enzymes. Research indicates that survivin expression is typically absent in normal tissues, but it is present in tumor cells. Survivin is mainly expressed in the cytoplasm and nucleus, with its staining localized to these regions. Survivin is positively expressed in pale yellow, brownish yellow, and tan hues. The subsequent scoring criteria were implemented for both primary and metastatic lymph nodes: Based on the percentage of positive cells, four grades were established: 0-10% corresponds to 0 points, 10-25% to 1 point, 25-50% to 2 points, and 51-100% to 3 points. The dyeing intensity is categorized into three levels: light dyeing is assigned 1-point, medium dyeing is assigned 2 points, and strong dyeing is assigned 3 points. The percentage of positive cells and staining intensity scores were amalgamated: scores of 0-1 were deemed negative, 2-3 as weak positive, 4-5 as positive, and 6 as strong positive. When the rating of metastatic lymph nodes was inferior to that of the primary site, it was determined that the expression of metastatic lymph nodes was downregulated.

Statistical analysis

The Chi-square test or Fisher's exact test was employed to analyze counting data and four-cell table data. Spearman's rank correlation was used to examine the correlation between the two-level variables. The three-year survival rate was assessed using the Kaplan-Meier method. All statistical analyses were conducted utilizing SPSS version 22.0 software.

Results

E-cadherin expression

The positive expression rate of E-cadherin in primary lesions was significantly elevated in patients with medium-to-high differentiation compared to those with low differentiation, suggesting a statistically significant difference ($P<0.05$). No significant correlation was observed between E-cadherin expression and sex, age, tumor size, or depth of invasion in the primary lesions ($P>0.05$) (**Table 1**). The reexpression rate of E-cadherin in metastatic lymph nodes was significantly higher in patients with

Table 2. Relationship between E-cadherin re-expression and different histopathological features in metastatic lymph nodes

Variant	N	E-cadherin re-expression		P
		-	+	
Gender				
Male	39	28	11	
Female	8	5	3	>0.05
Age				
<60	18	14	4	
≥60	29	19	10	>0.05
Differentiated degree				
Poor differentiation	27	24	3	
Medium-high differentiation	20	9	11	<0.05
Depth of invasion				
Not Full-thickness	8	6	2	
Full-thickness	39	27	12	>0.05
Size				
<5 CM	32	21	11	
≥5 CM	15	12	3	>0.05

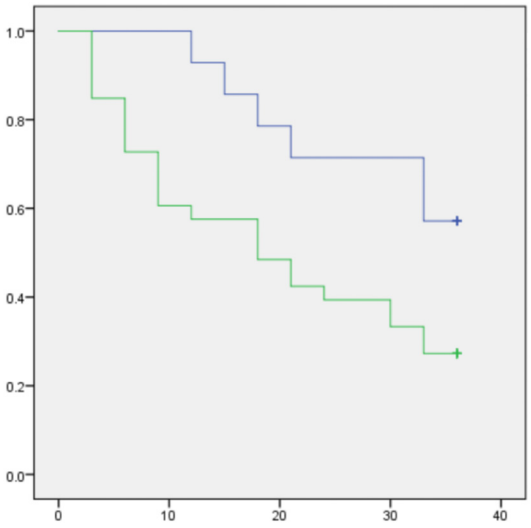

Figure 1. Comparison of survival time between E-cadherin re-expression positive group (the blue line) and negative group (the green line).

high differentiation than in those with low differentiation (P<0.05). In metastatic lymph nodes, no significant correlation was found between E-cadherin reexpression and sex, age, tumor size, or depth of invasion (P>0.05) (**Table 2** and **Figure 3**).

Survivin expression

In the primary lesions, the expression rate of Survivin was markedly elevated in patients with low differentiation compared to those with medium differentiation, exhibiting a statistically significant difference (P<0.05). However, Survivin expression in primary lesions did not exhibit a significant correlation with sex, age, tumor size, or depth of invasion (P>0.05) (**Table 3**). In metastatic lymph nodes, the incidence of downregulated Survivin expression was greater in patients with high differentiation than in those with low differentiation, exhibiting a statistically significant difference (P<0.05). Moreover, in metastatic lymph nodes, the downregulation of Survivin expression showed no significant correlation with sex, age, tumor size, or depth of invasion (P>0.05) (**Table 4** and **Figure 4**).

Of the 47 metastatic lymph nodes, 6 cases showed reexpression of E-cadherin alongside downregulation of Survivin. Spearman rank correlation analysis revealed a positive correlation between E-cadherin reexpression and Survivin downregulation (r = 0.279, P<0.05) (**Table 5**). In the group of 14 patients showing positive E-cadherin reexpression, the median survival duration was 36 months, with a 3-year survival rate of 57.1%. Conversely, among the 33 patients exhibiting negative E-cadherin reexpression, the median survival duration was 18 months, with a 3-year survival rate of 27%. The difference between the two groups was statistically significant (P<0.05) (**Figure 1**). Eleven patients exhibiting downregulated Survivin expression had a median survival duration of 33 months and a 3-year survival rate of 36.4%. The median survival time for the 36 patients showing negative downregulated Survivin expression was 24 months, accompanied by a 3-year survival rate of 36.1%. The difference between these two groups was not statistically significant (P>0.05) (**Figure 2**).

Discussion

The presence or absence of metastasis in malignant tumors is a recognized prognostic

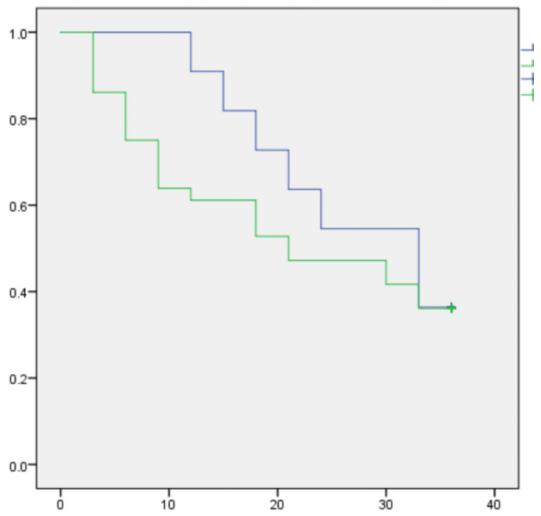

Figure 2. Comparison of survival time between positive (the blue line) and negative groups (the green line) with Survivin down-expression.

indicator. In the metastasis of malignant tumors, metastasis-promoting genes and metastasis-suppressor genes play opposing roles. Following metastatic promotion, tumor cells that previously lacked metastatic capability may develop some degree of metastatic potential. In contrast to oncogenes, which enhance tumorigenesis by modulating tumor cell proliferation, metastasis-suppressor genes do not affect tumor cell growth but rather impede the metastatic process [4].

E-cadherin, a transmembrane adhesion molecule, is a crucial element of the cadherin system, vital for sustaining intercellular adhesion in epithelial tissues, maintaining cell polarity, and ensuring epithelial stratification [5-7]. The CDH1 gene, situated on chromosome 16q22.1, encodes E-cadherin and comprises 15 introns and 16 exons. Research indicates that CDH1 expression is influenced by genetic modifications, microRNAs, and transcription factors, resulting in the downregulation of E-cadherin [8]. Recent studies have examined the correlation between E-cadherin expression and metastasis across multiple cancers, including esophageal cancer [9, 10], gastric cancer [11-13], endometrial cancer [14], colorectal cancer [15, 16], lung cancer [17], and bladder cancer [18].

This study examined E-cadherin expression in 47 cases of primary and metastatic lymph nodes from patients with advanced gastric carcinoma through immunohistochemistry. We analyzed the expression of E-cadherin in primary tumors and metastatic lymph nodes. In the primary lesions, E-cadherin exhibited positive expression in 4 out of 47 cases, whereas 43 cases demonstrated negative expression, yielding a positive expression rate of 8.5%. This indicates that E-cadherin is crucial in the detachment of tumor cells from the primary site. E-cadherin expression was detected in 0 patients with low differentiation and 4 patients with high differentiation among the subjects. The distinction between low-differentiation and high-differentiation patients was statistically significant ($P<0.05$). E-cadherin reexpression was noted in 14 cases of metastatic lymph nodes, suggesting that certain metastatic lymph nodes may display tumor cells regaining adhesion through E-cadherin reexpression. The reexpression of E-cadherin was significantly correlated with the level of tumor differentiation. The reexpression rate in the medium-to-highly differentiated group was significantly higher compared to the low-differentiated group, indicating that tumor cells in metastatic lymph nodes with greater differentiation may possess an increased propensity to restore their adhesion capability. No substantial correlation was identified between E-cadherin reexpression in metastatic lymph nodes and age, sex, tumor size, or depth of invasion, suggesting that these factors exerted no significant impact on E-cadherin reexpression.

Survivin is a protein regulated by the cell cycle, predominantly expressed during the G2/M phase. It is a brief polypeptide consisting of 142 amino acid residues. Survivin is typically absent in most terminally differentiated normal cells but is highly expressed in embryonic tissues and the majority of human cancers, including gastric carcinoma. Survivin is essential in regulating cell division, preventing apoptosis, and facilitating angiogenesis [19]. Survivin expression is undetectable in normal tissues but is present in tumor cells. Survivin is absent in normal gastric mucosal epithelial cells but is present in gastric cancer and precancerous lesions, exhibiting greater expression in cancerous lesions than in precancerous ones [20].

This study evaluated Survivin expression in 47 instances of primary and metastatic lymph nodes from patients with advanced gastric car-

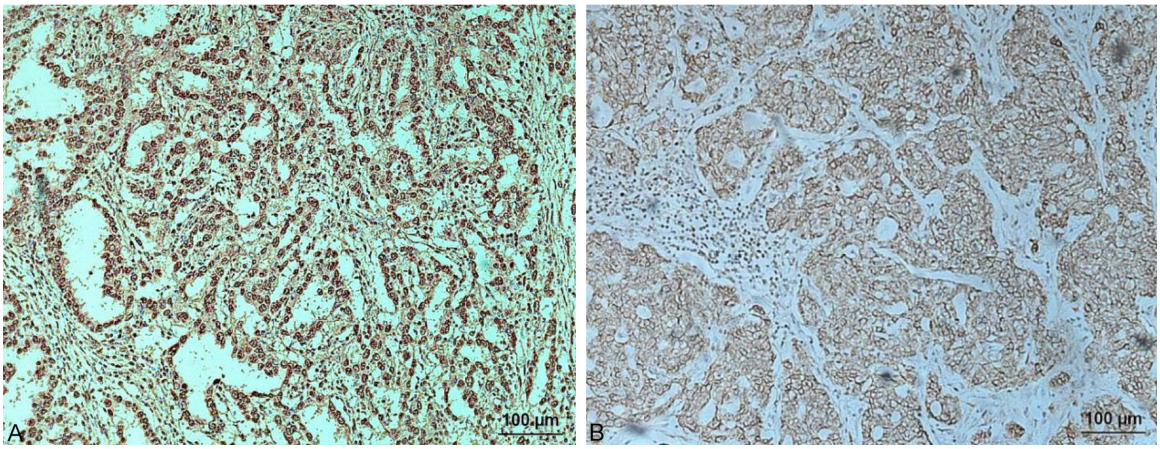

Figure 3. Expression of E-cadherin in primary lesions of advanced gastric carcinoma (A) and re-expression in metastatic lymph nodes (B) (SP×100).

Table 3. Relationship between Survivin expression and different histopathological features in primary lesions of advanced gastric carcinoma

Variant	N	Survivin		P
		-	+	
Gender				
Male	39	9	30	
Female	8	2	6	>0.05
Age				
<60	18	6	12	
≥60	29	5	24	>0.05
Differentiated degree				
Poor differentiation	27	3	24	
Medium-high differentiation	20	8	12	<0.05
Depth of invasion				
Not Full-thickness	8	2	6	
Full-thickness	39	9	30	>0.05
Size				
<5 CM	32	8	24	
≥5 CM	15	3	12	>0.05

cinoma. Out of the 47 primary lesions, Survivin was positively expressed in 36 instances (76.6%) and negatively in 11 instances. Survivin expression was positive in 24 of 27 poorly differentiated cases and 12 of 20 moderately differentiated cases, suggesting a correlation between Survivin expression and tumor differentiation grade. In metastatic lymph nodes, 34 cases showed positive Survivin expression, while 13 cases exhibited negative expression (72.3%). Survivin expression was significantly downregulated in 15 instances, indicating a decrease in the malignant proliferation of tumor cells in certain metastatic lymph nodes. The downregulation of Survivin in metastatic lymph nodes may suggest a diminished malignant proliferation capacity relative to the primary tumor. However, the downregulation of Survivin in metastatic lymph nodes was not correlated with age, sex, tumor size, or depth of tumor invasion, indicating that these variables do not substantially affect Survivin downregulation or malignant proliferation in metastatic lymph nodes.

E-cadherin in epithelial cells facilitates stable cell-cell adhesion by forming complexes with catenin proteins (α-catenin, β-catenin, and γ-catenin), thereby anchoring cells to the cytoskeleton. Frixen et al. demonstrated that elevated intracellular E-cadherin antibody levels could augment cellular invasiveness. A proposed mechanism is that the downregulation of E-cadherin elevates the concentration of free β-catenin, enabling its binding to target genes and facilitating tumor invasion [21]. The Wnt/β-catenin signaling pathway is essential for tumor initiation and progression, governing cell proliferation, differentiation, and migration [22]. β-catenin is an essential element of the Wnt/β-catenin-Tcf/Lef signaling cascade, and Survivin is a downstream target of this cascade. Upregulation of

Table 4. Relationship between Survivin down-expression and different histopathological features in metastatic lymph nodes

Variant	N	Survivin down-expression		P
		-	+	
Gender				
Male	39	28	11	
Female	8	4	4	>0.05
Age				
<60	18	11	7	
≥60	29	21	8	>0.05
Differentiated degree				
Poor differentiation	27	22	5	
Medium-high differentiation	20	10	10	<0.05
Depth of invasion				
Not Full-thickness	8	6	2	
Full-thickness	39	26	13	>0.05
size				
<5 CM	32	23	9	
≥5 CM	15	9	6	>0.05

E-cadherin expression inhibits β-catenin levels, resulting in diminished Survivin expression and reduced malignant proliferation. Torres et al. discovered that E-cadherin and caveolin-1 collaborate to suppress Survivin expression, facilitating normal apoptosis and preserving the equilibrium of cell proliferation and apoptosis [23].

This study found a positive correlation between E-cadherin reexpression and Survivin downregulation in metastatic lymph nodes ($P<0.05$), indicating a potential synergistic effect between these two factors in advanced gastric cancer. The up-regulation of tumor cell adhesion and the reduction of malignant proliferation may exert a synergistic effect. It is hypothesized that the re-expression of E-cadherin may impede the re-shedding of tumor cells, while the downregulation of Survivin may suppress the proliferation of shed tumor cells, based on their roles in the development and progression of gastric cancer. In metastatic lymph nodes exhibiting low malignancy, certain tumor cells demonstrate enhanced adhesion capabilities and diminished malignant proliferation compared to the primary tumor, thereby attenuating the tumor cells' propensity to detach, disseminate, and proliferate malignantly within the metastatic lymph nodes. This suggests the down-regulation of Survivin expression in metastatic lymph nodes is more significantly affected by the reexpression of E-cadherin than by tumor malignancy. This study established that E-cadherin modulates Survivin expression in metastatic lymph nodes to a certain degree. However, the gene-level expression of both requires further investigation.

The Kaplan-Meier survival analysis indicated that the differentiation level of the primary tumor significantly influences the 3-year postoperative survival rate of patients with advanced gastric cancer, corroborating results from other studies. This investigation also involved Kaplan-Meier survival analysis for the reexpression of E-cadherin and the downregulation of Survivin in metastatic lymph nodes. Our findings shown that the reexpression of E-cadherin in metastatic lymph nodes correlated with enhanced 3-year postoperative survival rates. This suggests that the improved adhesion capacity of tumor cells in the E-cadherin-positive cohort may impede their re-shedding and subsequent metastasis, potentially diminishing the primary cause of mortality linked to advanced malignancies. Therefore, the reexpression of E-cadherin in metastatic lymph nodes may function as a significant prognostic marker for advanced gastric cancer. The downregulation of Survivin expression in metastatic lymph nodes did not significantly affect the 3-year survival rate postsurgery. Therefore, Survivin does not seem to serve as an independent prognostic indicator for advanced gastric cancer, highlighting the intricacies of the tumor microenvironment and the presence of tumor heterogeneity.

Contemporary targeted therapies frequently concentrate on the particular expression of oncogenes at the primary tumor location. Tumor heterogeneity indicates that the biological traits of tumor cells in metastatic lymph nodes may differ from those in the primary tumor. Consequently, investigating the changes in metastasis potential and malignant proliferation of tumor cells in metastatic lymph nodes is essential for enhancing the efficacy and thoroughness of cancer treatment. The unique bio-

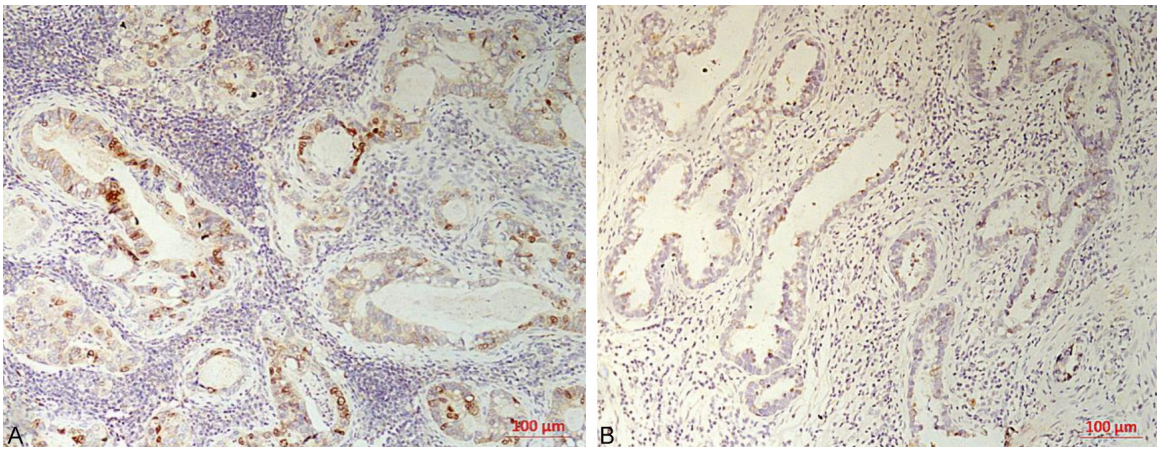

Figure 4. Survivin expression in primary gastric carcinoma (A) and down-regulated expression in metastatic lymph nodes (B) (SP×100).

Table 5. Correlation between E-cadherin re-expression and Survivin down-expression in lymph nodes with advanced gastric cancer metastasis

E-cadherin	Survivin		Total	r	P
	(+)	(-)			
(+)	6	8	14	0.279	<0.05
(-)	9	24	33		
Total	15	32	47		

logical characteristics of tumor cells in metastatic lymph nodes, in contrast to those in the primary tumor, underscore the intricacy of the tumor microenvironment, influenced by various interacting factors. The effectiveness of single-target drugs directed at the primary tumor is currently inadequate for treating metastatic lymph nodes. This study examined the changes in adhesion capacity and malignant growth of tumor cells in primary lesions and metastatic lymph nodes, along with their associations with clinicopathological parameters, patient survival, and prognosis. These findings offer novel insights that may enhance future treatment strategies for advanced gastric cancer.

The immunohistochemical staining results in this study were evaluated using semi-quantitative methods, which could be enhanced by more precise quantitative analysis techniques in future research. This study exclusively analyzed the expression of E-cadherin and Survivin at the protein level, necessitating further research at the gene level. In future studies, we will further evaluate the expression of E-cadherin and Survivin in advanced gastric cancer at the gene level and in animal experiments, in order to obtain more precise clinical significance.

In summary, E-cadherin and Survivin are crucial in the progression, invasion, and metastasis of advanced gastric cancer. The identification of E-cadherin and Survivin expression in primary and metastatic lymph nodes may provide considerable clinical insight for evaluating treatment response and prognostic outcomes in patients with advanced gastric cancer.

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Disclosure of conflict of interest

None.

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References

[1] Machlowska J, Baj J, Sitarz M, Maciejewski R and Sitarz R. Gastric cancer: epidemiology, risk factors, classification, genomic characteristics and treatment strategies. Int J Mol Sci 2020; 21: 4012.

[2] Jin X, Liu Z, Yang D, Yin K and Chang X. Recent progress and future perspectives of immuno-

therapy in advanced gastric cancer. Front Immunol 2022; 13: 948647.
[3] Danilewicz M, Stasikowska-Kanicka O and Wągrowska-Danilewicz M. Augmented immunoexpression of survivin correlates with parameters of aggressiveness in prostate cancer. Pol J Pathol 2015; 66: 44-48.
[4] Kodura MA and Souchelnytskyi S. Breast carcinoma metastasis suppressor gene 1 (BRMS1): update on its role as the suppressor of cancer metastases. Cancer Metastasis Rev 2015; 34: 611-8.
[5] Qiu J, Sun M, Wang Y and Chen B. Identification of hub genes and pathways in gastric adenocarcinoma based on bioinformatics analysis. Med Sci Monit 2020; 26: e920261.
[6] Läubli H and Borsig L. Altered cell adhesion and glycosylation promote cancer immune suppression and metastasis. Front Immunol 2019; 10: 2120.
[7] Stepan AE, Pirici D, Bălăşoiu M, Novac MB, Drocaş AI, Ciurea RN, Stepan D, Gheonea DI and Simionescu CE. E-cadherin/CD44 immunophenotype in the epithelial-mesenchymal transition of bladder urothelial carcinomas. Rom J Morphol Embryol 2015; 56: 85-91.
[8] Mareel M and Leroy A. Clinical, cellular and molecular aspects of cancer invasion. Physiol Rev 2003; 83: 337-376.
[9] Devaux CA, Mezouar S and Mege JL. The E-cadherin cleavage associated to pathogenic bacteria infections can favor bacterial invasion and transmigration, dysregulation of the immune response and cancer induction in humans. Front Microbiol 2019; 10: 2598.
[10] Autenshlyus AI, Bernado AV, Studenikina AA, Proskura AV, Davletova KI, Zhurakovskiy IP, Arkhipov SA, Varaksin NA, Sidorov SV and Lyakhovich VV. Personalized approach to determination of histidine-rich glycoprotein and E-cadherin in supernatants of immunocompetent blood cells and breast biopsy specimens in breast malignant and non-malignant disease. Dokl Biochem Biophys 2020; 490: 1-4.
[11] Saito T, Chambers JK, Nakashima K, Nibe K, Ohno K, Tsujimoto H, Uchida K and Nakayama H. Immunohistochemical analysis of beta-catenin, E-cadherin and p53 in canine gastrointestinal epithelial tumors. J Vet Med Sci 2020; 82: 1277-1286.
[12] Yonemura Y, Ishibashi H, Mizumoto A, Tukiyama G, Liu Y, Wakama S, Sako S, Takao N, Kitai T, Katayama K, Kamada Y, Taniguchi K, Fujimoto D, Endou Y and Miura M. The development of peritoneal metastasis from gastric cancer and rationale of treatment according to the mechanism. J Clin Med 2022; 11: 458.
[13] He Z, Duan X and Zeng G. Identification of potential biomarkers and pivotal biological pathways for prostate cancer using bioinformatics analysis methods. PeerJ 2019; 7: e7872.
[14] Jayaraman M, En N, V L and Harikrishnan V. A retrospective study on the expression of E-cadherin in endometrial carcinoma. Cureus 2024; 16: e70767.
[15] Ng L, Yu WS, Aung NM, Leung P, Luk JM, Wong DA, Sun S and Foo DC. Tissue cadherin 17 (CDH17): an important prognostic determinant of colorectal cancer using digital image analysis. Cancer Rep (Hoboken) 2024; 7: e70069.
[16] Kinsella AR, Green B, Lepts GC, Hill CL, Bowie G and Taylor BA. The role of the cell-cell adhesion molecule E-cadherin in large bowel tumor cell invasion and metastasis. Br J Cancer 1993; 67: 904-909.
[17] Schulz-Kuhnt A, Wirtz S, Neurath MF and Atreya I. Regulation of human innate lymphoid cells in the context of mucosal inflammation. Front Immunol 2020; 11: 1062.
[18] Singh R, Singh UP, Agrawal V and Garg M. Epithelial-to-mesenchymal transition based diagnostic and prognostic signature markers in non-muscle invasive and muscle invasive bladder cancer patients. Mol Biol Rep 2022; 49: 7541-7556.
[19] Liu YB, Zhang L, Guo YX, Gao LF, Liu XC, Zhao LJ, Guo BF, Zhao LJ, Zhao XJ and Xu DQ. Plasmid-based Survivin shRNA and GRIM-19 carried by attenuated salmonella suppresses tumor cell growth. Asian J Androl 2012; 14: 536-45.
[20] Kania J, Konturek SJ, Marlicz K, Hahn EG and Konturek PC. Expression of Survivin and caspase-3 in gastric cancer. Dig Dis Sci 2003; 48: 266-71.
[21] Ma B, Wheeler SE, Clark AM, Whaley DL, Yang M and Wells A. Liver protects metastatic prostate cancer from induced death by activating E-cadherin signaling. Hepatology 2016; 64: 1725-1742.
[22] Yu J, Tao Q, Cheng YY, Lee KY, Ng SS, Cheung KF, Tian L, Rha SY, Neumann U, Röcken C, Ebert MP, Chan FK and Sung JJ. Promoter methylation of the Wnt/beta-catenin signaling antagonist Dkk-3 is associated with poor survival in gastric cancer. Cancer 2009; 115: 49-60.
[23] Torres VA, Tapia JC, Rodriguez DA, Lladser A, Arredondo C, Leyton L and Quest AF. E-cadherin is required for caveolin-1-mediated down-regulation of the inhibitor of apoptosis protein survivin via reduced beta-catenin-Tcf/Lef-dependent transcription. Mol Cell Biol 2007; 27: 7703-7717.