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Impact of extranodal tumor deposits on prognosis and N stage in gastric cancer

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ABSTRACT

Background: Extranodal tumor deposits have been reported to be associated with a poor prognosis in many malignancies and are also included in the tumor, node, and metastasis staging system for colorectal cancer.
Methods: We reviewed retrospectively a total of 2,344 gastric cancer patients who underwent gastrectomy with curative intent at the Tianjin Medical University Cancer Institute and Hospital (Hexi District, Tianjin, China) and the First Affiliated Hospital of Hainan Medical University (Longhua District, Haikou, China). Patients were categorized into 2 groups based on extranodal tumor deposit status: a positive group, including those with extranodal tumor deposits, and a negative group composed of those with no extranodal tumor deposits. Clinicopathologic factors were correlated with extranodal tumor deposits, and their individual prognoses were analyzed. In addition, a pathologically modified node classification system was proposed by incorporating the extranodal tumor deposit status into the 8th ed of the N staging system. The superiority of prognostic prediction between the modified node classification and node stage was compared.
Results: A total of 645 (27.5%) patients had extranodal tumor deposits. The presence of extranodal tumor deposits was associated with a larger tumor size, Borrmann type III and IV, a deeper depth of invasion, and an advanced node stage. In the multivariate analysis, extranodal tumor deposits were an independent prognostic factor for gastric cancer patients after curative resection. Gastric cancer patients with extranodal tumor deposits demonstrated a lesser 5-year overall survival than those with no extranodal tumor deposits (31.9% vs 61.4%, $P < .001$). With the strata analysis, statistically significant prognostic differences between the two groups were only observed in patients at the N0-N2 stage. The modified node classification was found to be more appropriate for predicting the overall survival of gastric cancer patients after curative resection than node stage, and the −2 log likelihood of the modified node classification (16,042.890) was smaller than the value of node stage (16,150.811).
Conclusion: Extranodal tumor deposits in gastric cancer patients indicate aggressive characteristics and a poorer prognosis of gastric cancer. We maintain that extranodal tumor deposits should be incorporated into the N staging system to enhance the accuracy of the prognostic prediction of patients with gastric cancer.

Introduction

Extranodal tumor deposits (ETDs) are defined as irregular collections of discrete tumor cells in the soft tissue or fat that are discontinuous with the primary lesion. They show no evidence of residual lymph node tissue but are within the lymphatic drainage of the primary tumor. Some studies have suggested that such ETDs should be regarded as the primary tumor or a form of serosal invasion,[1,2] but others have argued that ETDs should be counted as positive lymph nodes.[3–11] ETDs have been reported in colorectal,[4–11] breast,[12] thyroid,[13] lung,[14] and gastric[15–18] carcinomas. ETDs have also been proven to be associated with decreased disease-free survival (DFS) and overall survival (OS).[3,15,16]

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The tumor, node, and metastasis (TNM) classification is used worldwide for cancer staging. It is an important factor in predicting prognosis and deciding the best treatment. ETDs have been incorporated into the category of lymph node metastasis in colon and rectal cancers. According to the eighth edition of the TNM staging system for colorectal carcinoma, an ETD in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues is defined as N1c for patients with no regional nodal metastasis.[19] For gastric cancer (GC), an ETD has been reported to be an independent prognostic factor in several studies,[3,15–18] but the impact of an ETD on the node (N) stages of the TNM staging system for GC has not been assessed. In this study, we analyzed retrospectively the outcomes of 2,344 GC patients who underwent some form of gastrectomy with curative intent. The aim of this study was to evaluate the potential impact of ETDs on the long-term outcomes of GC patients after curative gastrectomy and to test the superiority of our suggested modified N (mN) classification for prognostic prediction in GC compared with N stages of the 8th edition of the TNM staging system for GC.

Materials and Methods

Patients

The Ethics Committees of Tianjin Medical University Cancer Institute and Hospital (Hexi District, Tianjin, China) and the First Affiliated Hospital of Hainan Medical University (Longhua District, Haikou, China) reviewed and approved this study. All the patients signed an informed consent form. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee. At Tianjin Medical University Cancer Institute and Hospital, 3,253 patients with GC underwent surgical resection, and at the First Affiliated Hospital of Hainan Medical University, 755 patients with GC underwent surgical resection between January 2003 and December 2012, making them eligible for this study. The eligibility criteria for this study included the following: (1) patients with adenocarcinoma of the stomach, (2) patients who underwent gastrectomy with curative intent, (3) patients who received at least D1+ lymph node dissection, (4) patients who had more than 16 lymph nodes retrieved, (5) patients without distant metastasis, (6) patients with no history of gastrectomy or another malignancy, (7) patients with no history of neoadjuvant chemotherapy, (8) patients who were completely followed up, and (9) patients who did not die during the initial hospital stay or within 1 month postoperatively. Ultimately, 2,344 patients were enrolled in this study, including 2,033 from Tianjin Medical University Cancer Institute and Hospital and 312 patients from the First Affiliated Hospital of Hainan Medical University.

Evaluation of clinicopathologic variables and survival

The clinicopathologic features studied included the following 12 factors: sex, age at operation, tumor location, tumor size, Borrmann type, histology, depth of invasion, presence of lymph node metastasis, TNM stage, extent of lymphadenectomy, type of gastrectomy, postoperative chemotherapy, and ETD status. Factors related to survival were also analyzed.

All the patients underwent curative gastrectomy plus lymphadenectomy. Curative resection was defined as complete resection without microscopic disease in the margins and no evidence of distant metastasis. In the present study, an ETD was defined as the presence of cancer cells in the soft tissue that was discontinuous with the primary lesion or in perigastric soft tissue distinct from a lymph node or in the area of locoregional lymph node stations. Tumor deposits located on the peritoneal surfaces were not included as ETDs and were considered distant metastases. The ETDs were sorted together with lymph nodes by surgeons from the fresh specimens and then further retrieved by pathologists from the fixed specimen. ETDs are retrieved together with lymph nodes as a solid structure that can be discriminated from adipose tissue in the areas of the perigastric and locoregional lymph nodes. For postoperative pathology, all resected specimens, including the retrieved lymph nodes and adipose tissue, were grouped according to lymph node stations, fixed in 10% formalin, embedded in paraffin, and stained with hematoxylin and eosin. The pathologic diagnosis was established by two professional pathologists. The tumors were staged according to the eighth edition of the Union for International Cancer Control (UICC) TNM classification system[20,21]; whereas lymphadenectomy and lymph node stations were defined according to the third English edition of the Japanese Classification of Gastric Carcinoma and the fourth English edition of the Japanese Gastric Cancer Treatment Guidelines.[22,23] The tumors were classified into two groups based on histology: (1) differentiated type, including papillary, well, or moderately differentiated adenocarcinoma; and (2) undifferentiated type, including poorly differentiated or undifferentiated adenocarcinoma, signet-ring–cell carcinoma, and mucinous carcinoma.

Follow-up

The patients were followed up every 3 month for up to 2 years postoperatively, then every 6 months for up to 5 y, and then every year or until death. A physical examination, laboratory tests, and abdominal ultrasonography (US) were performed at each visit, whereas chest and abdominal computed tomography (CT) and endoscopy were obtained every 6 months or each year. The OS rate was calculated from the day of operation until the time of death or final follow-up. The median follow-up was 52 months (range: 1–115 months). The date of the final follow-up was December 30, 2017.

Statistical analysis

Categorical variables were analyzed by means of the χ^2 or Fisher exact test. Logistic regression analysis was used to determine the independent risk factors for the presence of ETDs. The OS curves were calculated using the Kaplan-Meier method based on the duration of time between the primary operative treatment and the final follow-up or death. The log-rank test was used to assess significant differences between curves. Independent prognostic factors were identified by the Cox proportional hazards regression model. To compare our suggested new definition of mN and a modified TNM (mTNM) stage with the eighth edition of TNM staging system, the −2 log likelihood, hazard ratio (HR) value, and 95% confidence interval (CI) related to the Cox regression model were used for measuring homogeneity and discriminatory ability. The statistical analysis was performed using the statistical analysis program package SPSS 18.0 (IBM Corp, Armonk, NY, USA).

Results

Clinicopathologic features

Of the 2,344, a total of 1,667 were men (71.1%) and 677 were women (28.9%). The patient age ranged from 20 to 89 years, and the median age was 60 years. The median OS of all patients after curative gastrectomy was 52 months, and the 5-year OS rate was 53.3%. Of the 2,344 GC patients who underwent curative gastrectomy, 1,788 patients underwent D2 or D2+ lymph node dissection, and 645 underwent D1+ dissection. The mean number of lymph nodes

Table I
Patient characteristics

Characteristics	ETD status, *n* (%)		χ^2	*P*
	Negative	Positive		
Sex			0.076	.782
Male	1,211 (72.6)	456 (27.4)		
Female	488 (72.1)	189 (27.9)		
Age (y)			3.698	.157
<50	310 (68.9)	140 (31.1)		
50~70	1,019 (73.2)	374 (26.8)		
≥70	370 (73.9)	131 (26.1)		
Tumor location			59.490	< .001
Lower one-third	679 (79.2)	178 (20.8)		
Middle one-third	384 (66.9)	190 (33.1)		
Upper one-third	440 (75.5)	143 (24.5)		
Two-thirds or more	196 (59.4)	134 (40.6)		
Tumor size			100.192	< .001
<5 cm	917 (82.2)	199 (17.8)		
≥5 cm	782 (63.7)	446 (36.3)		
Borrmann type			94.679	< .001
I, II	715 (84.4)	132 (15.6)		
III, IV	984 (65.7)	513 (34.3)		
Histology			22.339	< .001
Differentiated	463 (80.1)	115 (19.9)		
Undifferentiated	1,236 (70.0)	530 (30.0)		
Depth of invasion			195.608	< .001
T1	197 (97.0)	6 (3.0)		
T2	256 (94.1)	16 (5.9)		
T3	98 (79.7)	25 (20.3)		
T4a	1,118 (66.9)	552 (33.1)		
T4b	30 (39.5)	46 (60.5)		
N stage			322.539	< .001
N0	872 (89.6)	101 (10.4)		
N1	283 (69.7)	123 (30.3)		
N2	315 (65.4)	167 (34.6)		
N3a	181(52.0)	167 (48.0)		
N3b	48 (35.6)	87 (64.4)		
TNM stage			372.637	< .001
I	373 (96.6)	13 (3.4)		
II	586 (85.3)	101 (14.7)		
IIIA	502 (66.0)	259 (34.0)		
IIIB	188 (51.8)	175 (48.2)		
IIIC	50 (34.0)	97 (66.0)		
Postoperative chemotherapy			57.714	< .001
Yes	846 (66.1)	434 (33.9)		
No	853 (80.2)	211 (19.8)		
Type of gastrectomy			24.403	< .001
Subtotal	1,004 (76.5)	308 (23.5)		
Total	695 (67.3)	337 (32.7)		
Extent of lymphadenectomy			0.012	.914
D2 and D2+	1,295 (72.4)	493 (27.6)		
D1+	404 (72.7)	152 (27.3)		

ETD, extranodal tumor deposits.

dissected per patient was 27.9 ± 7.0. Of these patients, 1,280 received postoperative adjuvant chemotherapy with 5-fluorouracil, leucovorin and oxaliplatin (FOLFOX6); capecitabine and oxaliplatin (XELOX); S-1 and oxaliplatin (SOX); S-1; or capecitabine.

An ETD was detected in 645 (27.5%) of the 2,344 patients. The mean number of ETDs detected per patient was 1.6 (median 1, range 1–15). In the 645 patients with an ETD, 528 had only 1 ETD, and 117 patients had ≥2 ETDs. All patients were categorized into 2 groups according to ETD status: a positive group (PG)—those with an 1 or more ETDs—and a negative group (NG)—with no ETD. As a result, 645 patients were assigned to the PG, and 1,699 patients were assigned to the NG. Clinicopathologic variables were compared between the 2 groups, as presented in Table I. There were no significant differences in sex, age, or extent of lymphadenectomy between the 2 groups; whereas the incidence of an ETD was greater in patients with larger tumors (36.3% vs 17.8%, $P < .001$), Borrmann type III/IV (34.3% vs 15.6%, $P < .001$), a histologically undifferentiated type (30.0% vs 19.9%, $P < .001$), a deeper depth of invasion ($P < .001$), and advanced N ($P < .001$) and TNM stages ($P < .001$). In addition, tumor location was associated with ETDs ($P < .001$). Tumors located at the middle one-third and two-thirds or more of the stomach had a greater ratio of ETDs. Patients with ETDs were more likely to have undergone a total gastrectomy and postoperative chemotherapy than those with no ETDs. In the multivariate logistic analysis, tumor size (hazard ratio [HR]: 1.537, 95% confidence interval [CI]: 1.235–1.912, $P < .001$), Borrmann type (HR: 1.601, 95% CI: 1.260–2.035, $P < .001$), depth of invasion (HR: 1.867, 95% CI: 1.560–2.233, $P < .001$), and N stage (HR: 1.608, 95% CI: 1.483–1.744, $P < .001$) were identified as independent risk factors for the presence of ETDs.

Survival analysis of all GC patients

The results of the univariate and multivariate survival analyses are presented in Table II. The following 11 factors evaluated in the univariate analysis had a significant effect on survival: age at

Table II
The univariate and multivariate survival analyses of all patients with GC

Characteristics	Number of patients	5-y OS (%)	Univariate analysis		Multivariate analysis	
			χ^2	*P*	Hazard ratio (95% CI)	*P*
Sex			0.645	.422		
Male	1,667	52.9				
Female	677	54.2				
Age (y)			77.628	< .001		
<50	450	58.1			1 (ref)	
50~70	1393	57.8			1.068 (0.905–1.262)	.435
≥70	501	36.7			1.535(1.263–1.865)	< .001
Tumor location			90.464	< .001		
Lower one-third	857	65.1			1 (ref)	
Middle one-third	574	50.4			1.092 (0.915–1.903)	.328
Upper one-third	583	45.7			1.198 (0.980–1.465)	.077
Two-thirds or more	330	41.2			1.065 (0.850–1.334)	.585
Tumor size			139.862	< .001		
<5 cm	1,116	65.1			1 (ref)	
≥5 cm	1,228	42.6			1.192 (1.042–1.364)	.011
Borrmann type			67.653	< .001		
I/II	847	64.7			1 (ref)	
III/IV	1,497	46.8			1.193 (1.037–1.373)	.014
Histology			4.850	.028		
Differentiated	578	57.6			1(ref)	
Undifferentiated	1,766	51.9			1.030 (0.889–1.193)	.692
Depth of invasion			230.794	< .001		
T1	203	91.0			1(ref)	
T2	272	78.2			2.429 (1.142–4.179)	.001
T3	123	59.1			3.601 (2.056–6.308)	< .001
T4a	1,670	45.3			4.506 (2.728–7.442)	< .001
T4b	76	30.0			6.745 (3.800–11.971)	< .001
Lymph node metastasis			505.617	< .001		
N0	973	74.6			1(ref)	
N1	406	53.3			1.669 (1.380–2.019)	< .001
N2	482	38.3			2.136 (1.790–2.550)	< .001
N3a	348	29.0			2.710 (2.238–3.282)	< .001
N3b	135	16.8			4.231 (3.315–5.440)	< .001
Postoperative chemotherapy			6.953	.008		
Yes	1,280	54.9			1 (ref)	
No	1,064	51.5			1.654 (1.446–1.891)	< .001
Type of gastrectomy			101.529	< .001		
Subtotal	1,312	61.8			1 (ref)	
Total	1,032	42.5			1.157 (0.986–1.357)	.073
Extent of lymphadenectomy			37.841	< .001		
D2 and D2+	1,788	56.6			1 (ref)	
D1+	556	42.6			1.179 (1.027–1.352)	.019
ETD status			225.737	< .001		
Negative	1,699	61.4			1 (ref)	
Positive	645	31.9			1.473 (1.289–1.682)	< .001

Ref, reference category.

operation, tumor location, tumor size (<5 cm vs ≥5 cm), Borrmann type (type I and II versus type III and IV), histology (differentiated versus undifferentiated), depth of invasion, lymph node metastasis, postoperative chemotherapy, type of gastrectomy, extent of lymphadenectomy, and ETD status. GC patients with ETDs had a lesser 5-year OS than those with no ETDs (5-year OS: 31.9% vs 61.4%, $P < .001$, Fig 1, *A*). The analysis of patients grouped according to the number of ETDs revealed that the number of ETDs was associated with a worse prognosis ($P < .001$; Fig 1, *B*). In the multivariate analysis, ETD status (HR was 1.473 for PG, $P < .001$) was found to be an independent prognostic factor for OS, as follows: age at operation (≥70 years), tumor size (≥5 cm), Borrmann type (III and IV), depth of invasion, lymph node metastasis, postoperative chemotherapy, and extent of lymphadenectomy.

Incorporation of the ETD status into the eighth edition UICC N staging system

With the strata analysis, the significant prognostic differences between the two groups were observed in patients at the N0-N2 stages. An ETD did not affect the OS of patients with N3a and N3b disease (Figs 2, *A–E*). The OS of ETD-positive patients at the N0 and N1 stages was similar to that of patients at the N2 stage with no ETDs, and there were no significant survival differences between ETD-positive patients at the N2 stage and those at the N3a stage (Fig 2, *F*). According to the results of the stratified analysis, we incorporated ETDs into the eighth edition of the N staging system and introduced our newly modified N stages (mN, Table III). The mN stages were defined as follows: mN0, no regional lymph node metastasis and no ETD; mN1, 1-2 regional lymph node metastases and no ETD; mN2, 3-6 regional lymph node metastases and no ETD or 0-2 regional lymph node metastases and an ETD; mN3a, 7-15 regional lymph node metastases regardless of ETDs or 3-6 regional lymph node metastases and an ETD; and mN3b, 16 or more regional lymph node metastases regardless of ETDs.

The prognostic values of the N stage, mN stage, TNM stage, and mTNM stage were evaluated by univariate and multivariate analyses. In the mTNM stages, the 5-year OS rates were 78.4%, 59.2%, 41.4%, 29.6%, and 16.8%% in the mN0, mN1, mN2, mN3a, and mN3b stages, respectively ($\chi^2 = 575.130$, $P < .001$). In the TNM stages, the

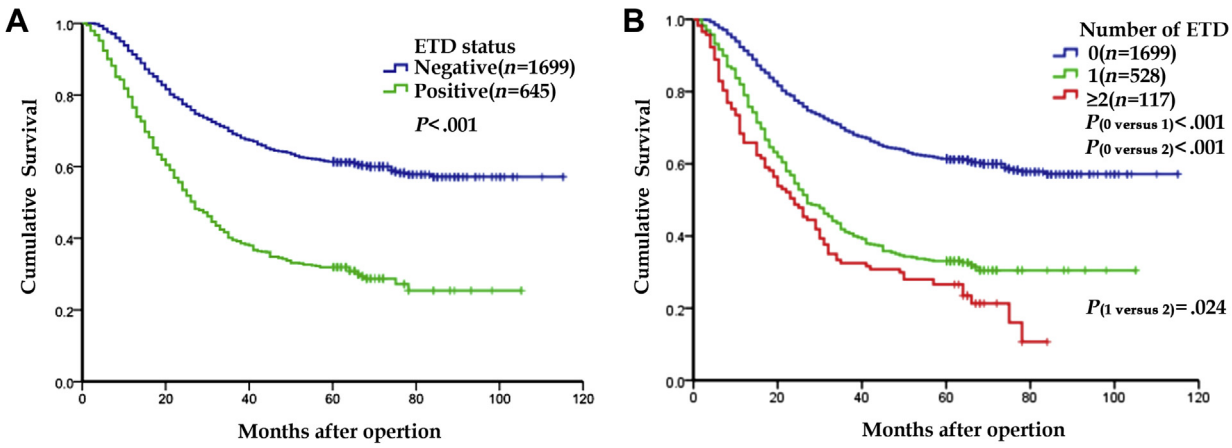

Fig 1. Overall survival curves after curative resection. (*A*) Patients with or without an ETD ($P < .001$, log-rank test). (*B*) Patients grouped according to the number of ETDs ($P < .001$).

5-year OS rates were 74.6%, 53.3%, 38.3%, 29.0%, and 16.8% in the N0, N1, N2, N3a, and N3b stages, respectively ($\chi^2 = 505.617$, $P < .001$; Table IV, Figs 3, *A*, *B*). The differences in prognostic prediction between the eighth edition of the N staging system and the mN classification system were compared directly. The mN classification system (HR = 1.727, 95% CI: 1.636–1.793, $P < .001$) was confirmed to be a more accurate prognostic classification for predicting the OS of GC patients after curative resection than the eighth edition of the N staging system (HR = 1.610, 95% CI: 1.541–1.682, $P < .001$). The −2 log likelihood of the mN stage was 16,042.890, which was less than the value of the N stage (16,150.811). Finally, we established an mTNM staging system by replacing the N stage with the mN stage according to the eighth edition of the UICC TNM staging system. As presented in Fig 4, the largest subgroup in the 2 staging systems is IIIA, whereas stage migration is most obvious in the IIIB subgroup. Survival curves according to stage grouping in the 2 systems reflect the difference in patient distribution: the mTNM grouping widens the distance between the curves, thus better stratifying the survival probabilities (Figs 3, *C*, *D*). The 5-year OS rates were 89.3%, 70.1%, 44.8%, 30.3% and 16.6% in mTNM stages I, II, IIIA, IIIB, and IIIC, respectively ($\chi^2 = 601.153$, $P < .001$). The predictive capacity of OS was also compared between the mTNM and TNM staging systems. We found that the mTNM staging system could better predict OS compared with the TNM staging system. The −2 log likelihood of the mTNM stage was 15,986.200, which was less than the value of the TNM stage (16,081.949; Table IV).

Prognostic value of mN staging system in the multivariate analysis

The mN stage and factors associated with OS in the univariate analysis were included in the multivariate analysis again. This time, age at operation, tumor size, Borrmann type (III and IV), depth of invasion, extent of lymphadenectomy, postoperative chemotherapy, and mN stage were found to be independent prognostic factors for OS. The ETD status and N stage were not significant in the multivariate analysis (*P* was 0.067 and 0.782, respectively; Table V).

Discussion

Many investigators have reported that the presence of an ETD is significantly associated with decreased OS and DFS for many kinds of malignancies, including GC.[1–18] Several studies have investigated the clinical importance of ETDs in patients with GC and affirmed that the presence of an ETD plays an important role in the prognosis of GC.[1–3,15–18] A viable question, however, is: Should an ETD, as an independent prognostic factor, be included in the TNM staging system and regarded as a part of primary tumor or lymph node? Controversy still exists. Anup et al[2] found that the OS rate of GC patients with an ETD was similar to that of stage T4 disease and thus suggested that the presence of an ETD should be considered a form of serosal invasion and included in the TNM staging system. Jiang et al[3] reported that an ETD was a significant independent predictor of decreased DFS and OS in GC patients and suggested that it be incorporated into the N stage. In the present study, we found that serosal invasion, lymph node metastasis, tumor size, and Borrmann type were independent risk factors for the presence of an ETD and that the OS of GC patients with an ETD at stage N0 and N1 was similar to that those at stage N2 without an ETD, and the OS of patients at stage N2 with an ETD was similar to that of patients at stage N3a. Although the ETD status was an independent prognostic factor for the entire study series, it did not affect the OS of GC patients at the stages of N3a and N3b stages. After incorporation of the ETD status into the N staging system, the mN category and mTNM staging system could better predict prognosis for GC patients after curative resection than the eighth edition of the UICC TNM staging system.

Until now, there has been no standard definition of an ETD. According to the eighth edition of the TNM staging system for colorectal cancer,[19] ETDs are irregularly discrete tumor deposits in the pericolic or perirectal fat that show no evidence of residual lymph node tissue but are within the lymphatic drainage of the primary tumor. The incidence of an ETD has been reported to be approximately 10% to 27% in GC.[1–3,15–18] In the present study, an ETD was defined as the presence of cancer cells in the soft tissue that was discontinuous with the primary lesion or in perigastric soft tissue distinct from lymph nodes, and an ETD was detected in 645 (27.5%) of the 2,344 patients, consistent with other reports.

No consensus has yet been reached on the mechanism of the development of ETDs. Some researchers consider it to originate from extracapsular extensions of a lymph node metastasis or the overgrowth of cancers from invading lymphovascular bundles because they found a significant correlation between ETDs and the incidence of lymph node metastasis.[6–10] Others, however, have argued that tumor cells released from a primary lesion that spread directly into the extranodal and extramural spaces explain the origin of ETDs.[17,18] According to our data, the presence of an ETD was independently associated with larger tumors, Borrmann type III/IV, deeper tumor invasion, and advanced lymph node stage in the logistic regression analysis. We believe that, for tumors without

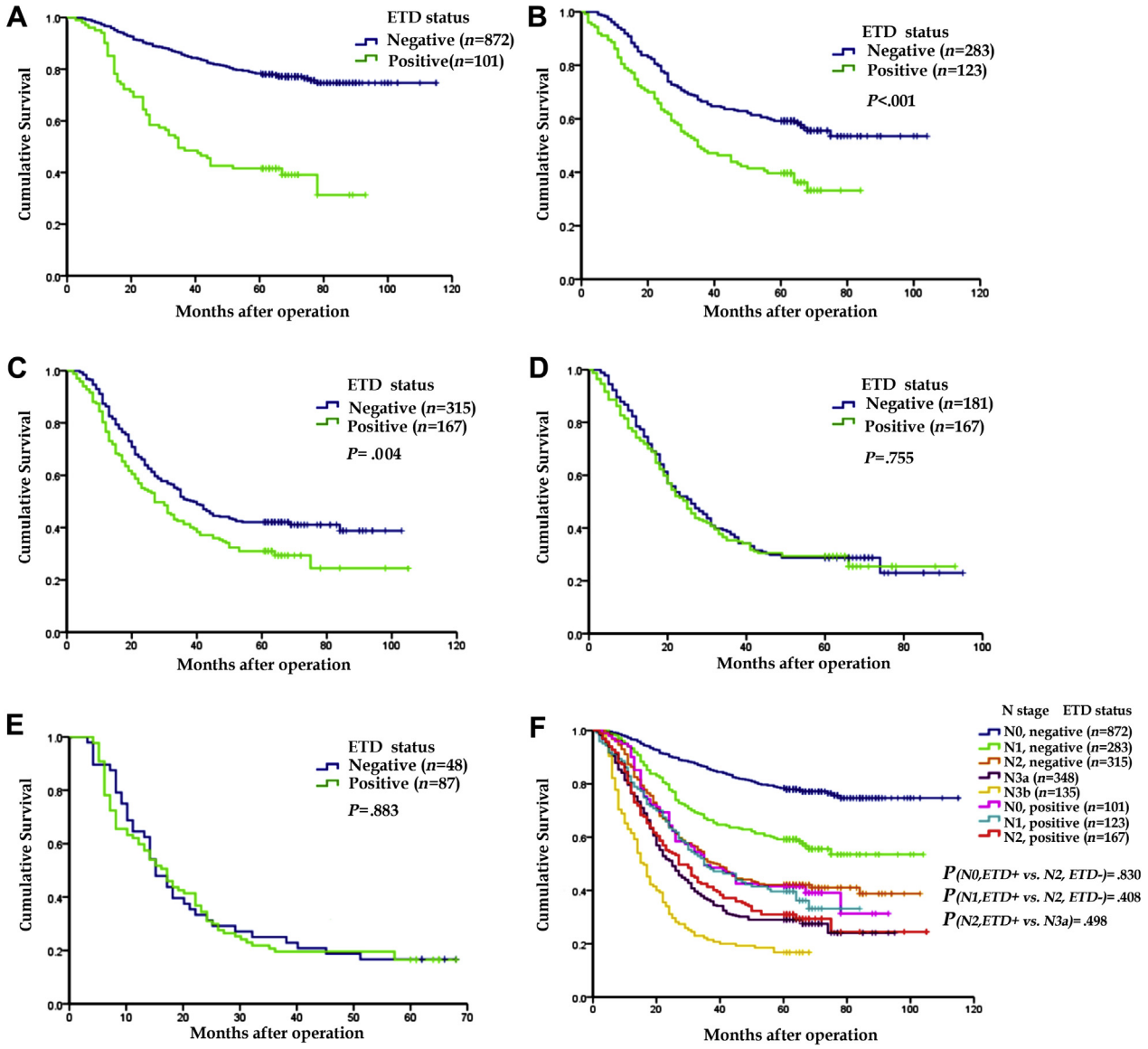

Fig 2. Overall survival curves stratified by N stage. The survival differences were only observed in GC patients with stages N0, N1, and N2 disease. (*A*) Stage N0. (*B*) Stage N1. (*C*) Stage N2. (*D*) Stage N3a. (*E*) Stage N3b. (*F*) Overall survival curves of GC patients according to the N stage and ETD status. The OS of ETD-positive patients at the stages N0 and N1 was similar to that of patients at the stage N2 without ETDs, and there were no significant survival differences between ETD-positive patients at the stage N2 and those at the stage N3a.

Table III
GC patients were divided into two groups according to the ETD status: A negative group and a positive group

ETD status	N0	N1	N2	N3a	N3b
Negative	mN0	mN1	mN2	mN3a	mN3b
Positive	mN2	mN2	mN3a	mN3a	mN3b

The ETD status was incorporated into the eighth ed of N staging system and composed the newly modified N (mN) stage.

serosal invasion, lymph node metastasis plays a major role in ETD formation, and for those with serosal invasion, both release of any cell seeding and lymph node metastasis correlate with ETDs. The presence of an ETD is a significant indicator of cancer aggressiveness, and such patients should be closely followed-up and treated more seriously.

As for the prognostic value of an ETD, earlier studies have confirmed the positive influence of ETDs on survival for various types of malignancies.[1–18] In our study, GC patients with ETDs demonstrated a significantly worse survival than those with no ETDs, and ETDs were found to be an independent prognostic factor in the multivariate analysis (HR: 1.473, 95% CI: 1.289–1.682, $P <$ .001). Although the 5-year OS rate decreased as the number of ETDs increased, the decrease was not linear, and a sharp slope was noted in survival curves if only 1 ETD was present. This is in accordance with another study that indicated that an ETD more closely resembled peritoneal metastasis than lymph node metastasis.[18] Nevertheless, many GC patients with an ETD had long-term survival, which was different from those with peritoneal disease. These results indicate that an ETD is a nonnegligible factor that cannot be ignored for predicting prognosis and determining treatment strategies after curative procedures and treatments. The TNM classification of GC is the most important prognostic indicator and is considered a key clue for treatment.[24] Nonetheless, whether an ETD should be incorporated into the TNM staging system for GC remains unclear. For colorectal cancers, tumors with an ETD are

Table IV
Definitions of N and TNM categories and their impact on the prognostic value of staging

Characteristics	Number of patients	5-y OS (%)	Univariate analysis		Multivariate analysis		−2log likelihood
			χ^2	*P*	HR (95% CI)	*P*	
N stage			505.617	< .001	1.610 (1.541–1.682)	< .001	1,6150.811
N0	973	74.6			1 (ref)		
N1	406	53.3			2.189 (1.819–2.634)	< .001	
N2	482	38.3			3.124 (2.642–3.694)	<.001	
N3a	348	29.0			4.362 (3.662–5.195)	< .001	
N3b	135	16.8			6.885 (5.505–8.611)	< .001	
mN stage			575.130	< .001	1.727 (1.636–1.793)	< .001	1,6042.890
mN0	872	78.4			1 (ref)		
mN1	283	59.2			2.183 (1.737–2.744)	< .001	
mN2	539	41.4			3.535 (2.887–4.327)	< .001	
mN3a	515	29.6			4.764 (4.033–5.628)	<. 001	
mN3b	135	16.8			8.520 (6.738–10.773)	< .001	
TNM stage			554.358	< .001	1.842 (1.747–1.943)	< .001	16,081.949
I	386	88.1			1 (ref)		
II	688	66.2			3.213 (2.357–4.380)	< .001	
IIIA	759	43.0			6.476 (4.806–8.726)	< .001	
IIIB	364	28.6			10.215 (7.505–13.905)	< .001	
IIIC	147	16.8			15.802 (11.299–22.098)	< .001	
mTNM stage			601.153	< .001	1.921 (1.814–2.027)	< .001	15,986.200
I	373	89.3			1 (ref)		
II	604	70.1			2.928 (2.092–4.099)	< .001	
IIIA	700	44.8			6.566 (4.748–9.080)	< .001	
IIIB	507	30.3			9.819 (7.157–13.471)	< .001	
IIIC	160	16.6			17.522 (12.404–24.752)	< .001	

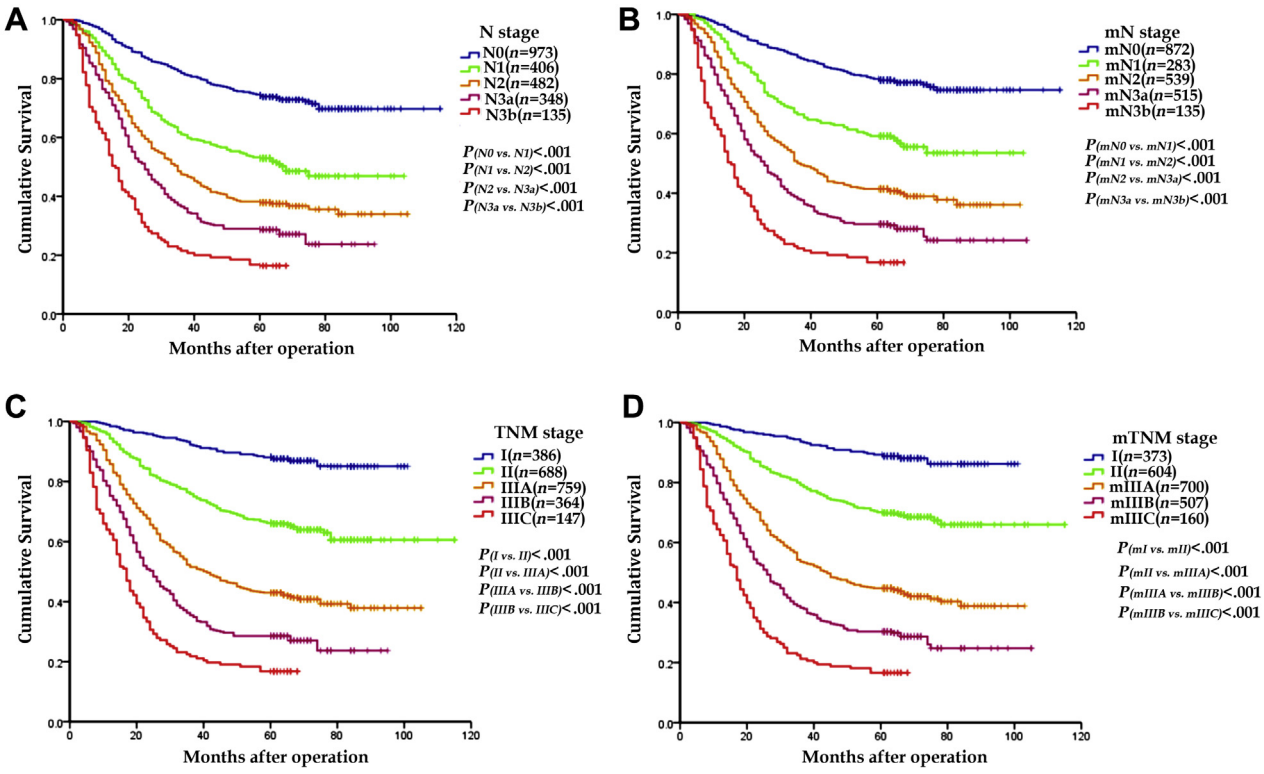

Fig 3. Overall survival curves of all GC patients. There were significant differences in OS with N, mN, TNM, or mTNM stage. (*A*) N stage. (*B*) mN stage. (*C*) TNM stage. (*D*) mTNM stage.

classified as N1c disease if no other lymph node metastasis has been detected.[19]

According to the strata analysis of the present study, the ETD status does not affect OS in patients with N3a and N3b disease, and, as for GC patients at stages N0, N1, and N2, those with an ETD had a significantly less 5-year OS than those with no ETD. In addition, the survival rates of ETD-positive patients at stages N0 and N1 were equal to those of stage N2 patients with no ETDs, and the OS of patients at stage N2with ETDs was similar to that of patients at N3a stage N3a. Based on these results, we incorporated the ETD status into the eighth edition of the UICC N staging system. Then, we proposed the use of the new mN stage to evaluate the prognostic value of the N stage and mN stage in GC. We found that the mN classification was a more accurate prognostic classification for

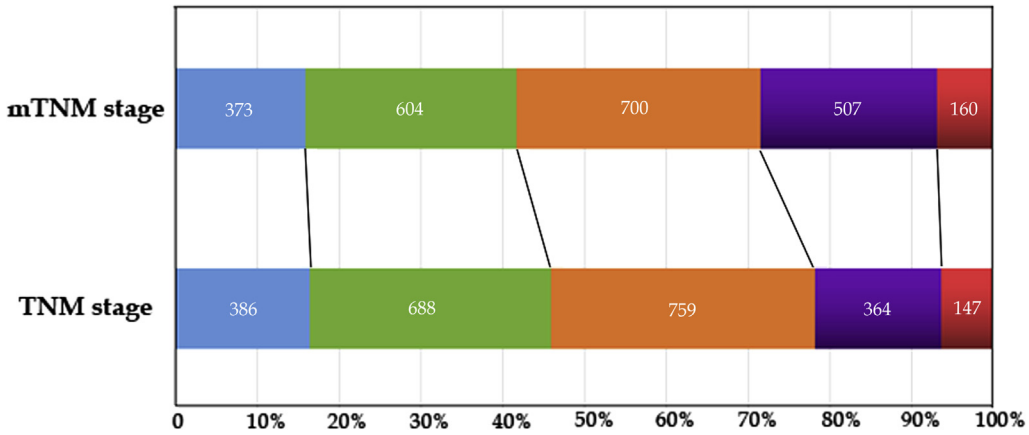

Fig 4. Patients distribution. The largest subgroup in the two staging system is IIIA, whereas the stage migration is most obvious in the IIIB subgroup.

Table V
Multivariate survival analysis of all GC patients after including mN stage

Factors		*P*	Hazard ratio	95% CI
Age (y)	<50/50–70/≥70	< .001	1.254	1.137–1.383
Tumor location	Lower one-third / middle one-third / Upper one-third / two-thirds or more	.495	1.025	0.955–1.100
Tumor size	<5 cm/≥5 cm	.009	1.190	1.044–1.357
Borrmann type	I,II / III,IV	.011	1.200	1.043–1.380
Depth of invasion	T1 / T2 / T3 / T4a / T4b	< .001	1.449	1.314–1.597
N stage	N0 / N1 / N2 / N3a / N3b	.782	1.025	0.863–1.117
Postoperative chemotherapy	Yes/no	< .001	1.664	1.460–1.897
Type of gastrectomy	Subtotal/total	.449	1.071	0.856–1.274
Extent of lymphadenectomy	D2 and D2 plus/D1+	.007	1.204	1.053–1.378
ETD status	Negative/positive	.067	1.158	0.990–1.353
mN stage	mN0/mN1/mN2/mN3a/mN3b	< .001	1.549	1.330–1.803

predicting the OS of GC patients after curative resection than the eighth edition of N classification. Furthermore, we established an mTNM staging system by replacing the N stage with the mN stage according to the eighth UICC TNM staging system, and the mTNM staging system was confirmed to be a better prognostic predictor compared with the TNM staging system. In our opinion, the presence of an ETD contains unique prognostic information that is not included in the TNM staging system, and the incorporation of the ETD status into the new revision of the N classification for GC can better predict the prognosis and then determine the treatment.

To verify the superiority of the incorporation of the ETD status into the N staging system, significant prognostic factors in the univariate analysis plus the mN stage were included in the multivariate survival analysis again. The mN stage remained a significant independent prognostic factor, and the ETD status and lymph node metastasis lost statistical significance. From this point of view, the mN stage is a better predictor of prognosis than the eighth edition of the UICC pN stage.

In conclusion, the presence of an ETD indicates aggressive characteristics of GC, such as serosal invasion, advanced N stage, larger tumor size, and an infiltrative macroscopic type. GC patients with an ETD have a poorer prognosis, and the survival of these patients at stages N0 and N1 are similar to that of patients at stage N2 with no ETD, and the OS of these patients at the stage N2 was equal to that of patients at the stage N3a. These results suggest that the en bloc clearance of adipose connective tissue in a D2 resection is crucially important. Pathologists should be aware of this clinically important feature and examine specimens from GC patient carefully to determine the presence of an ETD on histologic examination. In addition, ETD status should be recorded in the pathology report. Moreover, the presence of an ETD should be considered in GC staging. GC patients with an ETD should be closely followed-up and treated more seriously treated with adjuvant chemotherapy or radiotherapy.

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Conflict of interest

The authors declare that they have no conflict of interests.

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