Original Article

Extranodal soft tissue metastasis as an independent prognostic factor in gastric cancer patients aged under 70 years after curative gastrectomy

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Background: Accumulating evidence confirms the potential prognostic value of extranodal soft tissue metastasis (ESTM) in patients with solid cancers. The aim of this study was to elucidate the potential relationship between ESTM and lymph node (LN) metastasis, demonstrate clinicopathological predictive prognostic factors for ESTM and LN metastasis, and identify the prognostic value of ESTM for gastric cancer (GC) patients aged under 70 years.

Methods: A total of 580 GC patients who underwent the curative resection between 2003 and 2011 were included to identify if ESTM is essential to improve the accuracy of prognostic evaluation of the GC patients postoperatively. Overall survival rates were tested by Kaplan-Meier analysis. Univariate and multivariate analyses were applied to clarify the independent prognostic factors. Logistic regression analysis was adopted to clarify the risk factors for evaluating the presence of ESTM and LN metastasis. After cut-point survival analysis, the GC patients were divided into three subgroups based on the number of ESTM and then incorporated into the pTNM stage of gastric carcinoma to identify the possibility and necessity of incorporating ESTM into staging.

Results: ESTM was associated with advanced pT, pN and pTNM categories, large tumour size and the presence of signet-ring cell (SRC) variants. Survival analyses revealed that ESTM was associated with the OS and was an independent prognostic predictor in this GC patient cohort. Logistic regression analysis proved that ESTM and pT stage are significantly correlated with LN metastasis. Additionally, the ESTM was incorporated into the eighth edition of the pTNM classification and the prognostic evaluation of pTNME classification were calculated directly, and the results indicated that ESTM can reduce the stage migration.

Conclusions: ESTM is a significant independent predictor of survival in GC patients. To achieve R0 surgery, lymph nodes, soft tissues, fascia and adipose tissue should be resected en bloc at the same time as lymph node dissection. ESTM should be incorporated into pTNM staging according to the number retrieved from postoperative samples.

Keywords: Extranodal soft tissue; metastasis; neoplasm; prognosis; stomach

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Introduction

Despite a steady decrease in its incidence over the past several decades, gastric cancer (GC) remains the second most common cause of cancer-related death worldwide (1). Overall, assessment of patient characteristics to identify the risk of recurrence and poor prognosis is significantly crucial for choosing treatment strategies for cancer. To date, the extent of nodal involvement and the number of positive lymph nodes remain the focal point for determining the patient's prognosis. The tumour-node-metastasis (TNM) classification system is widely used for tumour staging and guides the treatment and prognostic predictions of patients with GC, yet patients with the same TNM stage show a wide range of survival times and outcomes. Extranodal soft tissue metastasis (ESTM), comprising cancer cells in soft tissue discontinuous with the primary lesion, is found during routine examination of approximately 10–28% of resected gastric carcinoma specimens (2), and the prognostic significance of extranodal tumour extension among solid cancers, including GC, thyroid carcinoma, rectal cancer, has been documented (3-8). The aim of this study was to evaluate the incidence and prognostic significance of ESTM in GC patients after curative resection. In addition, we classified ESTM into several different categories based on the cut-off value of the number of ESTM and then determined whether ESTM should be combined with the American Joint Committee on Cancer (AJCC) clinical (pTNM) staging system.

Methods

Patients and operative management

Between May 1, 2003, and June 31, 2011, a total of 657 GC patients who underwent curative resection at our institution were included in a retrospective database. All procedures were followed by the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. The inclusion criteria for this study were as follows: (I) pathologic diagnosis of primary adenocarcinoma of the stomach; (II) no Siewert type I or II oesophagogastric junction tumours; (III) no distant metastasis; (IV) pathologically negative resection margins (R0 resection); (V) no residual GC after surgery; (VI) no neoadjuvant chemotherapy or radiotherapy; (VII) no other synchronous malignancy or previous history of gastrectomy; (VIII) postoperative survival of at least 2 months; and (IX) under 70 years of age. In total, 580 patients met these criteria and were included. Primary tumours were resected en bloc by lymphadenectomy according to the guidelines of the Japanese Gastric Cancer Association (9), and the surgical procedures were mainly in accordance with the Japanese Gastric Cancer Treatment Guidelines (10). The TNM classification for GC (eighth edition) was adopted for the staging of all enrolled cases.

Follow-up

Patients were postoperatively followed up every 3–6 months for the first 2 years, every 6 months for the next 3 years, and annually thereafter until the end of the study (October 2016) or death. The median follow-up duration was 41.8 [2–136] months.

Pathological assessment

All specimens were analysed by two experienced pathologists, and different opinions were resolved through discussion to establish the ultimate diagnosis results. Carcinoma lesions along with the surrounding gastric wall were fixed in formalin and sectioned into multiple 5-mm slices in parallel with the lesser curvature. ESTM was defined as the presence of cancer cells in adipose tissue discontinuous with the primary lesion or in perinodal adipose tissue different from the lymph node (11) (*Figure 1*). The pathology report mainly included data regarding tumour size, ESTM, Lauren classification, depth of invasion (pT stage), number of regional LN metastases (pN stage), number of LNs examined (NELN), perineural invasion, lymphovascular invasion (LVI) and vascular invasion (VI).

Statistical analysis

The clinicopathologic features investigated for prognostic significance included gender, age, tumour size, tumour location, type of gastrectomy, Lauren classification, pT stage, pN stage, NELN, blood loss, lymphadenectomy, AJCC pathological stage (pTNM), perineural invasion, LVI, VI, signet-ring cell (SRC) variants, ESTM, blood loss and postoperative chemotherapy.

Clinicopathological characteristics significantly associated with patient survival were evaluated using the Kaplan Meier method and Cox proportional hazards analysis. Akaike information criterion (AIC) and Bayesian information criterion (BIC) values within a Cox

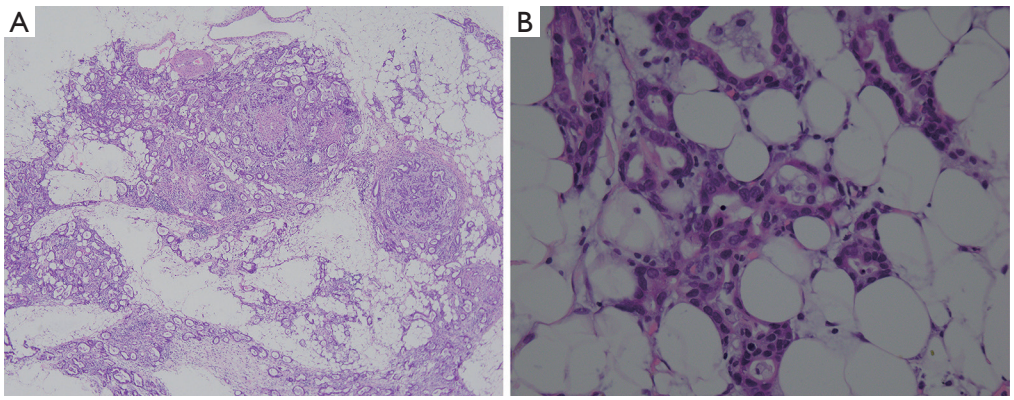

Figure 1 cancer cells deposit in adipose tissue discontinuous with the primary lesion (A: H&E, original magnifications ×40; B: H&E, original magnifications ×400).

proportional hazard regression model were calculated for each category to assess its discriminatory ability, whereby a smaller AIC or BIC value indicated a better model performance. Stratum analysis was applied to assess the influence of clinicopathological characteristics on the accuracy of the prognostic prediction of ESTM in GC patients. Differences in proportions of patients were analysed with the χ^2 test. Logistic regression analysis was adopted to clarify risk factors that predict the presence of ESTM and cut point survival analysis to identify the optimal cut off values for the ESTM count. The threshold for statistical significance was $P<0.05$. The statistical analysis was performed using IBM SPSS Statistics, version 22.0 (IBM Corp., Armonk, NY, USA).

Results

Overall, 580 patients with resected GC met the eligibility criteria. The age range of the patients included in this study was between 20 and 70 years. Among the patients examined, the absence of ESTM (ESTM–) was confirmed in 434, and the presence of ESTM (ESTM+) was confirmed in 146. The two groups (ESTM– and ESTM+) were balanced with reference to gender (P=0.575), age (P=0.593), tumour location (P=0.249), Lauren classification (P=0.924), type of gastrectomy (P=0.07), lymphadenectomy (P=0.144), NELN (P=0.651), perineural invasion (P=0.543), LVI (P=0.218), VI (P=0.690), blood loss (mL, P=0.817) and postoperative adjuvant chemotherapy (P=0.306). Simultaneously, significant differences in tumour size (P=0.006), pT category (P<0.001), pN stage (P<0.001), AJCC pathological stage (P<0.001) and signet ring cell variants (P=0.027) were observed between the ESTM negative and ESTM positive groups (*Table 1*).

Univariate and multivariate survival analyses of 580 GC patients

Univariate analysis revealed older age (age ≥65), advanced pT, pN, pTNM category, the presence of ESTM, LVI, VI and/or perineural invasion, the presence of SRC variants, larger tumour size (>4 cm), primary tumour invasion more than two-thirds of the stomach, Borrmann type IV GC, total gastrectomy and D1+ lymphadenectomy to be associated with a poor prognosis among GC patients. In the multivariable analysis, the variables of age, tumour size, pT stage, pN stage, pTNM stage, ESTM, VI, and SRC variants remained independent prognostic factors for the postoperative OS of all GC patients (*Table 2*). To measure discriminatory ability, AIC and BIC values were calculated for the independent predictors of OS. As ESTM showed the second smallest values, thus indicating that it was the better prognostic predictor of OS in this GC patients cohort (*Table 3*). Survival curves comparing age, tumour size, pT stage, pN stage, pTNM stage, VI and SRC variants are depicted in *Figure 2*.

For further illustration of the potential prognostic prediction ability of ESTM for GC patients, stratum analysis within the Kaplan-Meier was adopted. The prognosis for patients in the ESTM– and ESTM+ groups stratified by tumour size, pT stage, pN stage, SRC variants and VI was compared, and we found that the 5-year survival rate of patients with ESTM-positive tumours was lower than that for patients with ESTM-negative tumours. This

Table 1 Correlation between ESTM and clinicopathologic factors in gastric carcinoma patients following a curative resection

Characteristics	All patients (n=580)	ESTM		χ^2	P value*
		Negative (n=434)	Positive (n=146)		
Age (years)				0.286	0.593
<65	380	287	93		
≥65	200	147	53		
Gender				0.315	0.575
Male	404	305	99		
Female	176	129	47		
Tumor location				4.113	0.249
Upper third	126	95	31		
Middle third	62	46	16		
Lower third	262	204	58		
>2/3 stomach	130	89	41		
Tumor size (cm)				7.513	0.006
≤4	218	177	41		
>4	362	257	105		
Lauren classification				0.158	0.924
Intestinal	281	212	69		
Diffuse	282	209	73		
Mixed	17	13	4		
Bormann type				4.079	0.253
I	31	24	7		
II	178	141	37		
III	293	216	77		
IV	78	53	25		
Type of gastrectomy				5.322	0.070
TG	189	131	58		
PG	88	65	23		
DG	303	238	65		
Lymphadenectomy				2.213	0.144
D1+	75	51	24		
D2/D2+	505	383	122		
AJCC 8th T stage				50.002	<0.001
pT1	10	9	1		
pT2	69	68	1		
pT3	25	20	5		
pT4a	454	330	124		
pT4b	22	7	15		

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	All patients (n=580)	ESTM		χ^2	P value*
		Negative (n=434)	Positive (n=146)		
AJCC 8th N stage				79.803	<0.001
pN0	152	149	3		
pN1	97	72	25		
pN2	127	97	30		
pN3a	126	75	51		
pN3b	78	41	37		
NELN				0.828	0.651
≤15	6	5	1		
16–30	432	319	113		
>30	142	110	32		
AJCC 8th pathological stage				86.897	<0.001
IA	8	8	0		
IB	37	37	0		
IIA	24	19	5		
IIB	109	103	6		
IIIA	195	149	46		
IIIB	127	73	54		
IIIC	80	45	35		
Perineural invasion				0.370	0.543
No	566	425	141		
Yes	14	9	5		
Lymphovascular invasion				1.157	0.218
No	566	426	140		
Yes	14	8	6		
Vascular invasion				0.159	0.690
No	572	429	143		
Yes	8	5	3		
Signet-ring cell variant				4.911	0.027
No	546	414	132		
Yes	34	20	14		
Blood loss (mL)				0.054	0.817
<500	558	418	140		
≥500	22	16	6		

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	All patients (n=580)	ESTM		χ^2	P value*
		Negative (n=434)	Positive (n=146)		
Adjuvant chemotherapy				1.046	0.306
No	210	282	88		
Yes	370	152	58		

*, log-rank test. ESTM, extranodal soft tissues metastasis; TG, total gastrectomy; PG, proximal subtotal gastrectomy; DG, distal subtotal; NELN, number of examined lymph nodes.

Table 2 Clinicopathological characteristics and survival analyses of the cohort of 580 gastric cancer patients

Characteristics	No. of patients	5Y-OS (%)	Chi-square value†	Univariate (P value)	HR (95% CI)	Multivariate (P value)
Age (years)			6.312	0.012	1.360 (1.106–1.672)	0.004
<65	380	34.7				
≥65	200	26.0				
Gender			0.541	0.462		
Male	404	29.9				
Female	176	35.8				
Tumor location			13.608	0.003	1.080 (0.985–1.185)	0.101
Upper third	126	28.6				
Middle third	62	32.3				
Lower third	262	37.0				
>2/3 stomach	130	23.8				
Tumor size (cm)			33.224	<0.001	1.253 (1.011–1.555)	0.040
≤4	218	44.0				
>4	362	24.3				
Lauren classification			2.711	0.258		
Intestinal	281	32.4				
Diffuse	282	32.2				
Mixed	17	11.8				
Bormann type			17.486	<0.001	1.082 (0.945–1.240)	0.121
I	31	41.9				
II	178	33.7				
III	293	32.7				
IV	78	19.2				

Table 2 (*continued*)

Table 2 (*continued*)

Characteristics	No. of patients	5Y-OS (%)	Chi-square value†	Univariate (P value)	HR (95% CI)	Multivariate (P value)
Type of gastrectomy			17.774	<0.001	0.929 (0.829–1.041)	0.204
TG	189	24.3				
PG	88	28.4				
DG	303	37.3				
Lymphadenectomy			5.758	0.016		
D1+	75	20.0				
D2/D2+	505	33.4				
AJCC 8th T stage			65.704	<0.001	1.473 (1.373–1.518)	<0.001
pT1	10	80.0				
pT2	69	60.9				
pT3	25	40.0				
pT4a	454	26.9				
pT4b	22	9.1				
AJCC 8th N stage			130.305	<0.001	1.143 (1.017–1.761)	0.011
pN0	152	55.2				
pN1	97	40.2				
pN2	127	26.8				
pN3a	126	17.5				
pN3b	78	6.4				
ESTM			64.840	<0.001	1.468 (1.169–1.844)	0.001
Yes	146	13.0				
No	434	38.0				
NELN			3.196	0.202		
≤15	6	50.0				
16–30	432	30.1				
>30	142	35.9				
AJCC 8th pathological stage			145.136	<0.001	1.439 (1.322–1.567)	<0.001
IA	8	85.7				
IB	37	67.6				
IIA	24	62.5				
IIB	109	47.7				
IIIA	195	29.7				
IIIB	127	15.7				
IIIC	80	7.5				

Table 2 (*continued*)

Table 2 (*continued*)

Characteristics	No. of patients	5Y-OS (%)	Chi-square value†	Univariate (P value)	HR (95% CI)	Multivariate (P value)
Perineural invasion			9.132	<0.001	1.105 (0.599–2.038)	0.749
No	566	32.1				
Yes	14	14.3				
Lymphovascular invasion			13.160	<0.001	1.626 (0.918–2.880)	0.095
No	566	32.3				
Yes	14	7.1				
Vascular invasion			13.518	<0.001	5.036 (2.260–11.222)	<0.001
No	572	32.3				
Yes	8	0				
Signet-ring cell variant			13.267	<0.001	1.620 (1.101–2.386)	0.014
No	546	33.3				
Yes	34	5.9				
Blood loss (Ml)			0.409	0.522		
<500	558	31.4				
≥500	22	45.5				
Adjuvant chemotherapy			0.022	0.882		
No	210	29.7				
Yes	370	35.2				

†, log-rank test; HR, hazard ratio; 95% CI, 95% confidence; Y, year; OS, overall survival; ESTM, extranodal soft tissues metastasis; NELN, number of examined lymph node.

Table 3 Test of the most intensively prognostic predictors of gastric cancer patients

Characteristics	AIC value	BIC value	-2log-likelihoodvalue	Chi-square value	The likelihood ratio test (P value)
Age (years)	209.321	296.581	169.321	4.483	0.034
Tumor size (cm)	207.530	294.791	167.530	2.693	0.101
AJCC 8th T stage	208.265	278.074	176.265	11.428	0.044
AJCC 8th N stage	213.008	287.179	179.008	14.171	0.007
ESTM	209.186	296.447	169.186	4.349	0.037
AJCC 8th TNM stage	211.965	277.411	181.965	17.128	0.009
Vascular invasion	216.007	303.338	176.077	11.240	0.001
Signet-ring cell variant	207.530	294.791	167.530	2.693	0.101

ESTM, extranodal soft tissues metastasis.

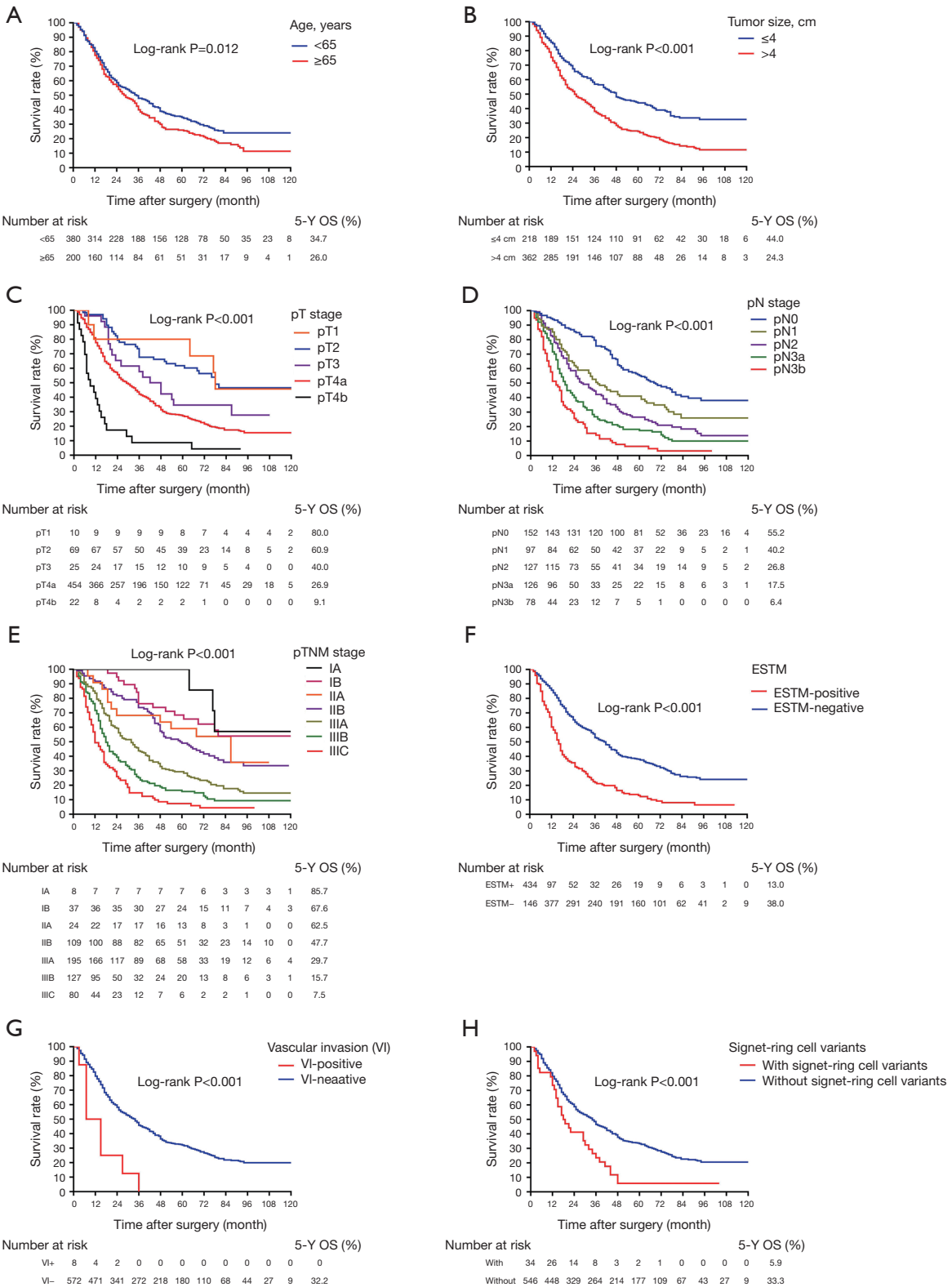

Figure 2 Survival curves of patients according to subgroups: (A) age at surgery; (B) tumour size; (C) pT stage; (D) pN stage; (E) pTNM stage; (F) ESTM; (G) vascular invasion; and (H) signet-ring cell variants.

was also true for the stratum categories of tumour size, SRC variants and VI (*Figure 3*).

Logistic regression analysis to identify risk factors predictive of ESTM and LN metastasis

Logistic regression analysis was applied to identify risk factors predicting ESTM, including tumour size, tumour location, Borrmann type, Lauren classification, perineural invasion, LVI, VI, SRC variants, pT stage, and pN stage, though only pT and pN stages were correlated significantly with ESTM (OR, 2.204; 95% CI, 1.407–3.452, P=0.001; OR, 1.749; 95% CI, 1.483–2.064, P<0.001, respectively) (*Table 4*). Further logistic regression analysis of risk factors predictive of LN metastasis, including tumour size, tumour location, Borrmann type, Lauren classification, perineural invasion, LVI, VI, SRC variants, pT stage, pT stage and ESTM indicated that tumour size (OR, 1.643; 95% CI, 1.077–2.507, P=0.021), ESTM (OR, 19.285; 95% CI, 6.002–61.973, P<0.001) and pT stage (OR, 1.748; 95% CI, 1.377–2.219, P<0.001) were significantly associated with LN metastasis (*Table 5*).

Incorporation of ESTM into the AJCC pTNM staging system (eighth edition) and stage migration analysis of ESTM

Cut point analysis was performed to determine the optimal ESTM count cut off values for discriminating survival differences among various subgroups, and the results are presented in *Table S1*. Appropriate ESTM count cut-off values to verify statistically significant survival differences among subgroups were identified as 0, 1–3, and ≥4. In addition, Kaplan Meier analysis indicated significant survival differences among these three ESTM count subgroups (P<0.001, *Figure 4A*). Additionally, the ESTM was incorporated into the eighth edition of the pTNM classification and the prognostic prediction of pTNME classification were calculated directly. No statistically significant survival differences were observed between pIIAE1-3 patients and pIIIAE0 patients (P=0.156; *Figure 4B*), or between pIIBE1-3 patients and pIIIAE0 patients (P=0.536; *Figure 4C*). Simultaneously, there were significant survival differences between pIIAE0 and pIIAE1-3 patients (P=0.011, *Figure 4D*), pIIBE0 and pIIBE1-3 patients (P=0.007, *Figure 4E*). Also, significant survival differences can be detected among the pIIIAE0, pIIIAE1-3 and pIIIAE ≥4 patients (P=0.003, *Figure 4F*); pIIIBE0, pIIIBE1-3 and pIIIBE ≥4 (P=0.002, *Figure 4G*), especially among pIIICE0, pIIICE1-3 and pIIICE ≥4 patients (P=0.004, *Figure 4H*). These results manifested that pTNME is a promising prognostic classification and might be an alteration of the eighth edition of pTNM classification; however, it requires further validations.

Discussion

The histologically complete resection (R0) of tumours is the only potentially curative treatment for patients with gastric carcinoma. The AJCC recommends curative gastrectomy with the systematic lymph node dissection up to second-tier nodes (D2) when tumours are confined to the primary lesion and regional lymph nodes (12). However, the significance of extranodal soft tissue in lymph node dissection has not been mentioned in all guidelines for GC, even though pathological examination of surgical specimens has revealed a rate of extranodal metastasis reaching 10% to 20% (2). Furthermore, previous studies have reported that ESTM is more likely to occur in large tumours, tumours with invasive growth characteristics, undifferentiated carcinoma, and lymph node, peritoneal, hepatic metastasis or recurrent lymphatic vessel metastasis (2,13).

To date, patient prognosis has primarily been predicted by the extent of nodal involvement and the number of metastasized lymph nodes (LNs). Indeed, the TNM classification system is widely used for tumour staging and guides treatment decisions and prognostic predictions of patients with cancer (1). However, patients with the same pTNM stage have a wide range of survival times and treatment outcomes. Localized disease often recurs after curative resection, even for pT1 tumours. Anticipating the prognosis of patients who undergo curative surgery, especially for early disease, is difficult, which implies that the current staging system is inaccurate for prognostic predictions and does not provide a good basis for adjuvant treatment decisions. A prognostic factor that can ascertain patients with a high risk of recurrence and death would be conducive to more accurately predict patient prognoses as well as elect GC patients who have a high risk of death and who might profit from adjuvant chemotherapy. To date, many histological and biological markers in addition to T and N have been reported and discussed as prognostic factors (14,15).

Recently, it has been suggested that extra-nodal involvement is related to an advanced stage and appears to be a reliable prognostic factor for GC (2-4,16). In addition,

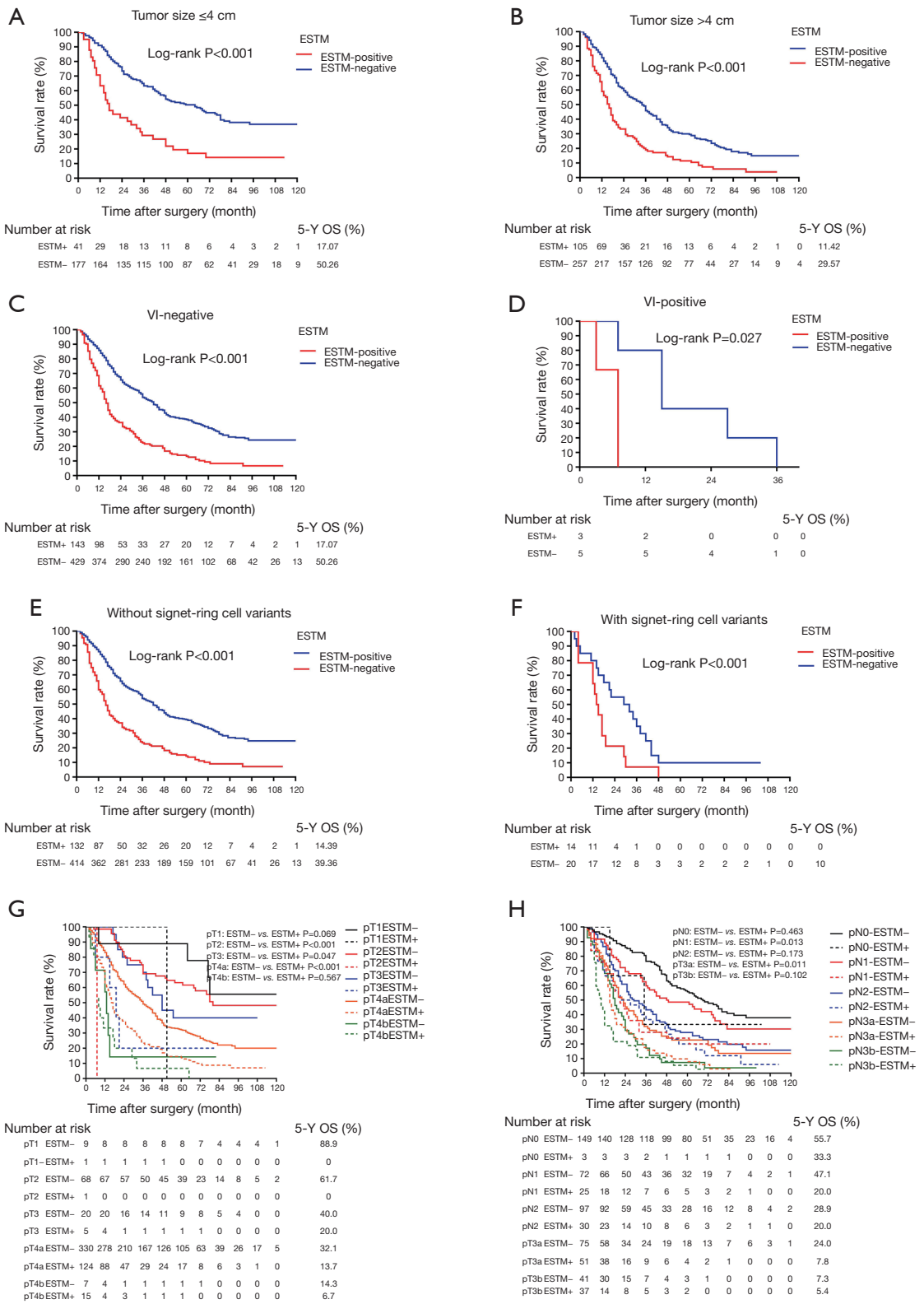

Figure 3 Survival curves between ESTM-positive group and ESTM-negative groups: (A) with tumor sizes <4 cm; (B) tumor sizes ≥4 cm; (C) VI-negative; (D) VI-positive; (E) without signet-ring cell variants; (F) with signet-ring cell variants; (G) with pT stage; (H) with pN stage.

Table 4 Logistic regression analysis of risk factors predicting the presence of ESTM

Characteristics	OR (95% CI)	Univariate P value	OR (95% CI)	Multivariate P value
Tumor location	1.099 (1.029–1.744)	0.005	–	–
Tumor size (cm)	1.082 (0.903–1.296)	0.036	1.308 (0.952–1.133)	0.399
Borrmann type	1.269 (0.987–1.631)	0.063	0.994 (0.735–1.345)	0.971
Lauren classification	1.044 (0.745–1.464)	0.801	–	–
Perineural invasion	1.675 (0.552–5.080)	0.363	–	–
Lymphovascular invasion	2.282 (0.778–6.691)	0.133	–	–
Vascular invasion	1.800 (0.425–7.626)	0.425	–	–
AJCC 8th T stage	2.919 (1.897–4.414)	<0.001	2.204 (1.407–3.452)	0.001
AJCC 8th N stage	1.914 (1.632–2.246)	<0.001	1.749 (1.483–2.064)	<0.001
Signet ring Cell Variant	2.195 (1.076–4.468)	0.030	1.601 (0.729–3.513)	0.241

ESTM, extranodal soft tissues metastasis; OR, odds ratio; 95% CI, 95% confidence interval.

Table 5 Logistic regression analysis of risk factors predicting the presence of LN metastasis

Characteristics	OR (95% CI)	Univariate P value	OR (95% CI)	Multivariate P value
Tumor location	1.099 (1.029–1.744)	0.005	0.932 (0.763–1.139)	0.493
Tumor size (cm)	2.335 (1.601–3.406)	<0.001	1.643 (1.077–2.507)	0.021
Borrmann type	1.269 (0.987–1.631)	0.063	–	–
Lauren classification	1.044 (0.745–1.464)	0.801	–	–
AJCC 8th T stage	2.216 (1.727–2.105)	<0.001	1.748 (1.377–2.219)	<0.001
ESTM	24.920 (7.809–79.529)	<0.001	19.285 (6.002–61.973)	<0.001
Perineural invasion	2.613 (0.479–9.779)	0.316	–	–
Lymphovascular invasion	4.730 (0.614–36.467)	0.136	–	–
Vascular invasion	1.066 (0.213–5.341)	0.938	–	–
Signet ring cell variant	2.137 (0.812–5.624)	0.124	–	–

LN, lymph node; OR, odds ratio; 95% CI, 95% confidence interval; ESTM, extranodal soft tissues metastasis.

previous studies have confirmed that ESTM, which is an intermediate between LN metastasis and peritoneal metastasis, is an independent factor influencing the prognosis of GC patients (17). What's more, a previous study also showed that extra-nodal extension was the significant prognostic factor in patients with early GC and nodal metastases (18). The researchers demonstrated that pT1 or pN1 GC patients with ESTM+ had a worse prognosis than those pT2 or pN2 patients without ESTM. Therefore, they suggested adjuvant therapy to be taken into consideration for GC patients in early stages with ESTM (18). However, most of previous studies have enrolled patients aged older than 80 years. As the average lifetime of men and women in China are 74 and 77 years old, respectively, results would not be as dependable if elderly patients older than these are evaluated (19,20). Moreover, death among patients older than 70 years within 5 years after the surgery may be wing to their own lifespans rather than due to recurrence of metastasis of GC; the 5-YSR of patients is also an important indicatrix for patients with cancer. Therefore, the patients with resected GC included in present study were aged under 70 years, which may have resulted in age selection bias.

In this study, we investigated the clinical parameters

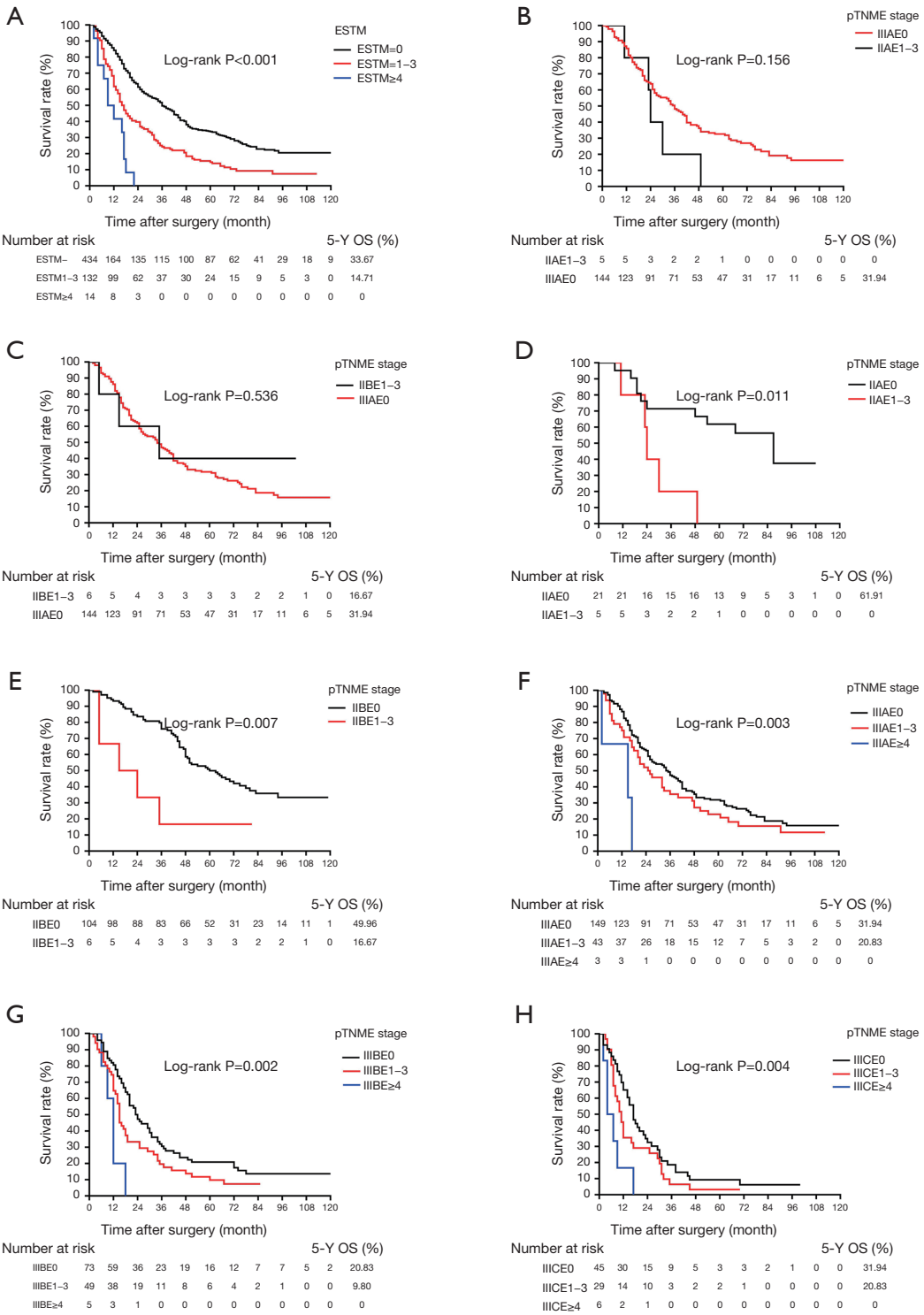

Figure 4 Survival curves of the different subgroups of patients according to (A) the number of ESTM; (B) survival curves comparing GC patients with pIIAE1-3 and pIIIAE0 stage; (C) survival curves comparing GC patients with pIIBE1-3 and pIIIAE0 stage; (D) survival curves comparing GC patients with pIIAE0 and pIIAE1-3 stage; (E) survival curves comparing GC patients with pIIBE0 and pIIBE1-3 stage; (F) survival curves comparing GC patients with pIIIAE0, pIIIAE1-3 and pIIIAE ≥4 stage; (G) survival curves comparing GC patients with pIIIBE0, pIIIBE1-3 and pIIIBE ≥4 stage; (H) survival curves comparing GC patients with pIIICE0, pIIICE1-3 and pIIICE ≥4 stage.

and prognostic value of ESTM in the GC patients who underwent radical resection, and we found that the incidence of ESTM was 146 (25.2%) among 580 patients. Our univariate and multivariate survival analyses indicated that tumour size, pT stage, pN stage, pTNM stage, ESTM, VI, and SRC variants are independent poor prognostic factors. Tumour size t4 cm, presence of ESTM, VI and SRC variants, higher pT stage, pN stage and pTNM stage were associated with a poorer 5Y-OS. It is generally known that different histotypes sometimes means different biological behaviour. In the literature, GC with SRC variants tends to metastasize to the peritoneum and has favorable prognosis in early stages but poor prognosis in advanced tumor stages in comparison to non-SRC adenocarcinoma (21,22). Therefore, the prognosis for patients in the ESTM– and ESTM+ groups stratified by SRC variants as well as other prognostic factors including tumour size, pT stage, pN stage, and VI was compared. And the results indicated that 5-YSR of patients in the ESTM group was significantly lower than that of patients without ESTM stratified by SRC variants as well as the other prognostic variables of tumour size and VI. These results demonstrated the ESTM might be considered as a common prognostic factor independent by histotypes, tumour size and VI.

Considering that pN stage is the most valuable prognostic indicator of GC patients, logistic regression analysis on risk factors that predict LN metastasis were performed (23,24), revealing a close relationship between LN metastasis with pT stage, tumour size and ESTM. Importantly, cancer patients with ESTM were at higher risk of LN metastasis. Our results emphasize the importance of ESTM in patient prognosis and its association with LN metastasis. ESTM can also be an efficient predictor of LN metastasis, and pT may be conducted as an indicator of ESTM. Thus, GC patients in an advanced pT stage may be at a higher risk of LN metastasis. Therefore, patients with advanced clinical T stage (cT stage) should be monitored more closely, and as many LNs as possible should be retrieved for accurate staging (25,26).

Likewise, the logistic regression analysis was also conducted to identify risk factors of the existence of ESTM and pT stage and pN stage were found to be important risk predictor of ESTM in this regard. Accordingly, ESTM patients with higher pT and pN stages may have a shorter survival time, which is in agreement with previous studies demonstrating that ESTM is closely associated with tumour aggressiveness (27,28). Our analysis results also foreground the important value of ESTM for prognosis and its relationship with LN metastasis and tumour invasion. ESTM may also be a valid predictor of LN metastasis. In view of these results, we propose that ESTM be included in the current pTNM staging system as an important prognostic factor.

Etoh *et al.* (3) have demonstrated that ESTM is an independent prognostic factor and should therefore be incorporated in the pTNM staging system. ESTM has been associated with a high recurrence risk, and was found to be a better prognostic factor than lymph node status (29). It is also reported an increasing number of positive lymph nodes with ESTM to be associated with poorer survival outcomes (3). In this study, outcomes were poorer with an increasing number of ESTMs. To identify whether ESTM should be included in the pTNM category, we stratified patients into three subgroups according to the cut-off analysis of ESTM number and incorporated ESTM into the eighth edition pTNM stage system. And this analysis showed the pTNME classification might reduce stage migration and might be a more appropriate prognostic classification for predicting the OS of GC patients after curative surgery than the eighth edition of pTNM classification, especially for advanced-stage GC. However, it requires further validations.

As there may be a tendency towards bias in a retrospective study, further multicentre, randomized controlled trials, especially utilizing postoperative pathology reports, are required.

Overall, our results demonstrated that incorporating ESTM into a new edition of the pTNM classification for GC might help offer better prognostic prediction. Accurate classification of lymphatic spread in the resected gastric specimens is crucial not only for estimating prognosis but also for stratifying patients in future clinical trials and for providing personalized adjuvant strategies, providing additional information for the AJCC pN category and pTNM stage. This approach will also be conducive to identifying GC patients with inferior prognoses. In future staging systems, the number of positive lymph nodes should be considered as well as also the presence of ESTM in GC. Therefore, lymph nodes, soft tissues, fascia and adipose tissue should be removed en bloc at the same time of lymph node dissection; only in this way can the purpose of R0 surgery be achieved.

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Footnote

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

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures were followed by the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions.

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Supplementary

Table S1 Prognostic effect in 580 GC patients depending on the cut-off number of ESTM

Cut-off number of ESTM	5Y-OS (%) between subgroups of patients	Chi-squire value	P value
1	19.0 *vs.* 6.3	5.936	*0.015*
2	16.3 *vs.* 0	6.804	*0.009*
3[†]	14.7 *vs.* 0	8.051	*0.005*
4	14.1 *vs.* 0	3.225	*0.073*
5	14.0 *vs.* 0	2.137	*0.144*
6	13.6 *vs.* 0	8.750	*0.003*

P values were calculated by the log-rank test for survival curves that were generated by the Kaplan-Meier method. Significant values ($P<0.05$) are in italic. [†], the most appropriate cut-off value of the number of ESTM was 3. Y, year; OS, overall survival; ESTM, extranodal soft tissues metastasis.