Original article

Impact of extranodal extension on prognosis in lymph node-positive gastric cancer

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Background: The TNM classification system is used widely for tumour staging, and directs the treatment and prognosis of patients with cancer. The aim of this study was to assess the prognostic value of extranodal extension (ENE) in patients with early gastric cancer.

Methods: All patients who underwent gastrectomy with lymphadenectomy for primary gastric cancer with lymph node metastases between January 2003 and June 2006 were reviewed. Histological slides of metastatic nodes were reviewed by two gastrointestinal pathologists. The association of ENE with clinicopathological characteristics was assessed. The disease-specific survival rate was calculated by the Kaplan–Meier method, and a multivariable Cox regression model was used to identify independent prognostic factors.

Results: Some 1143 patients were included. ENE was associated with advanced pT and pN category, larger tumour size and lymphovascular/perineural invasion. In multivariable analysis, pT category, pN category, ENE, lymphovascular invasion and perineural invasion were found to be independent prognostic factors in node-positive gastric carcinoma. The 5-year survival rate of patients with ENE was 48·1 per cent, compared with 78·2 per cent for patients without ENE ($P < 0{\cdot}001$). In the subgroup of patients with early gastric cancer, ENE was associated with a worse 5-year survival rate in patients with early (T1) gastric cancer: 75 per cent in patients with ENE *versus* 96·9 per cent in those without ($P < 0{\cdot}001$).

Conclusion: ENE is an independent prognostic factor in patients with early and advanced gastric cancer.

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Introduction

The TNM classification system is used widely for tumour staging, and directs the treatment and prognosis of patients with cancer[1]. However, patients in similar stage groups may have a different prognosis. For example, some patients with lymph node metastasis are cured by surgery, whereas in others disease recurs even after adjuvant therapy[2]. This implies that the current staging system is inaccurate for prognostication and does not provide a good basis for decisions regarding adjuvant treatment. A prognostic factor that can identify patients at high risk of recurrence would be helpful for more accurate prediction of prognosis, as well as for selecting patients with gastric carcinoma who are at high risk of recurrence and might benefit from adjuvant chemotherapy.

The seventh edition of the American Joint Committee on Cancer (AJCC) manual[1] uses the number of metastatic lymph nodes to determine N category. Other studies have reported on the location of metastatic nodes[3], the ratio of number of metastatic nodes to the total number of removed nodes[4], and the maximum diameter of metastatic lymph nodes[5] in order to refine nodal staging. In addition, several studies[6–11] have reported that extranodal extension (ENE) of metastatic lymph nodes is a poor prognostic indicator. Only a few studies have been performed regarding the prognostic value of ENE in gastric cancer. Most studies have reported on a small number of patients, or have used inconsistent definitions of ENE[12–15]. The aim of the present study was to investigate the prognostic significance of ENE in patients with node-positive gastric carcinoma.

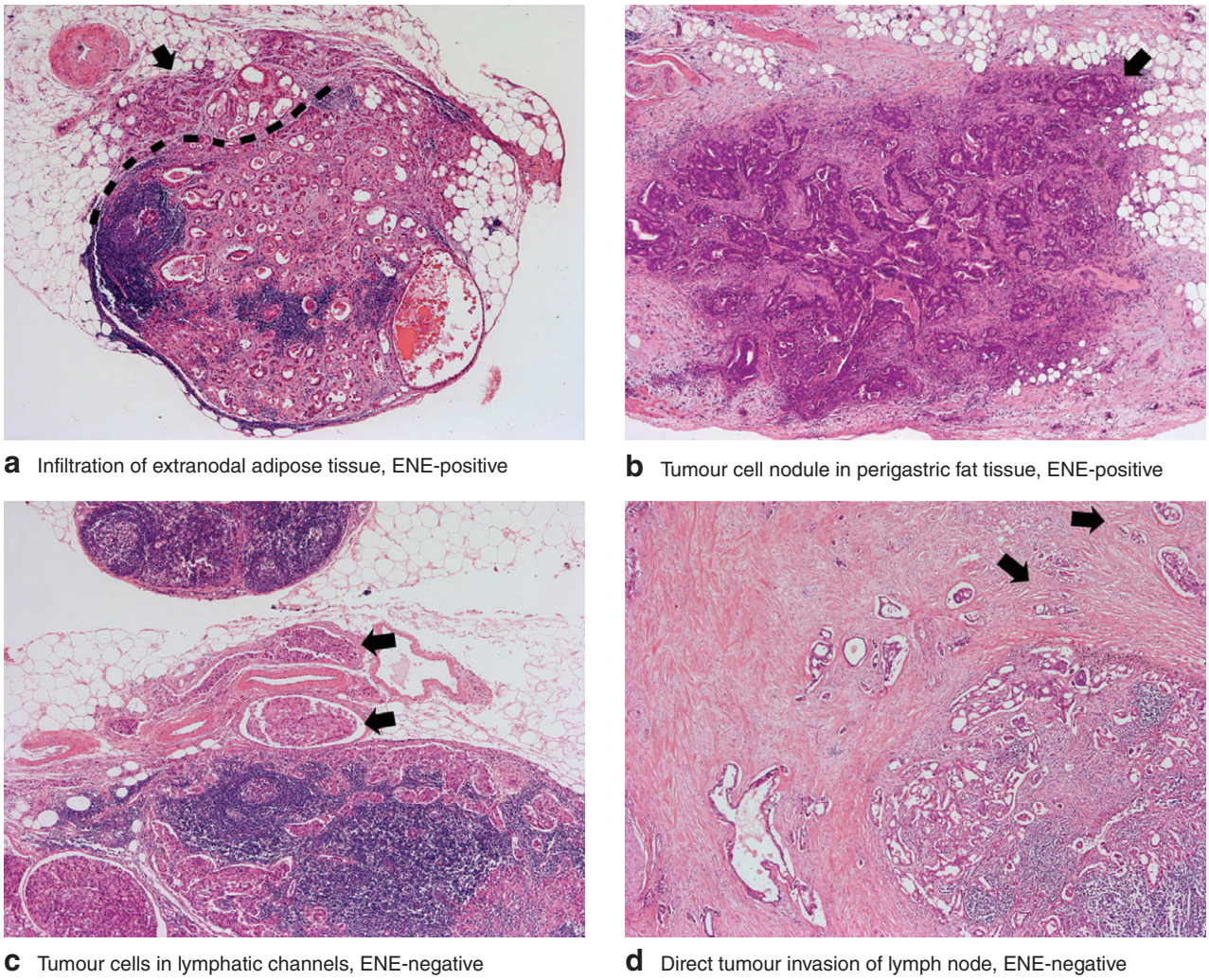


Fig. 1 Examples of extranodal extension (ENE) in lymph nodes of patients with gastric cancer (haematoxylin and eosin stain, original magnification × 40). **a** Tumour cells infiltrating adipose tissue (arrow) beyond the capsule of the lymph node (dotted line) (ENE-positive). **b** Although no definite lymphoid tissue is present, tumour cells have formed a nodule with adipose tissue infiltration (arrow) not continuous with the primary tumour (considered as ENE-positive). **c** Tumour cells identified in the lymphatic channels (arrows) outside the capsule of the lymph node were classified as ENE-negative. **d** Tumour cells identified beyond the lymph node capsule but in continuum with the primary tumour (arrows), suggesting direct invasion into the lymph node (ENE-negative)

Methods

The protocol for this retrospective cohort study was approved by the institutional review board of Asan Medical Centre, Seoul, Korea. All patients who underwent gastrectomy and lymphadenectomy for primary gastric carcinoma between January 2003 and June 2006 were selected from an institutional database. Patients who had received neoadjuvant chemotherapy or radiotherapy, those with tumours in the remnant stomach after previous partial gastrectomy, those with recurrent gastric cancers and patients with fewer than 15 lymph nodes removed were excluded. The medical records were reviewed to determine patients' demographics, clinical and pathological characteristics, including age, sex, American Society of Anesthesiologists (ASA) score, co-morbidities, preoperative albumin level, tumour location, size, gross appearance according to the Japanese Gastric Cancer Association[3] or Bormann type, differentiation grade, Laurén classification, depth of invasion, total number of removed nodes and number of metastatic lymph nodes, lymphovascular

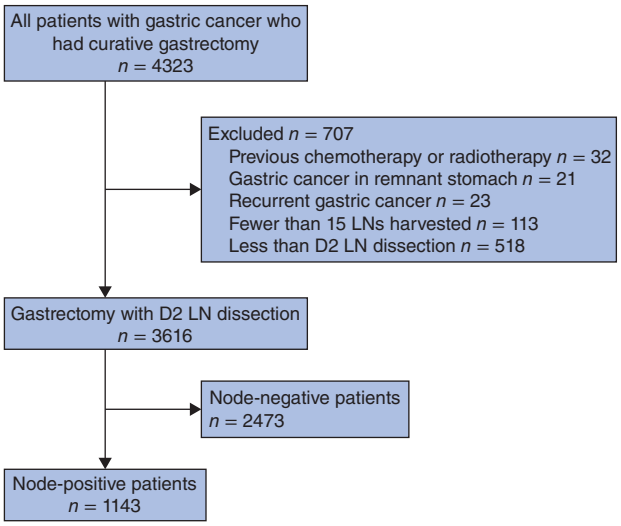


Fig. 2 Flow chart showing the selection of patients with node-positive gastric carcinoma. LN, lymph node

invasion, perineural invasion and adjuvant chemotherapy. Follow-up was to 30 June 2013. Patients lost during follow-up or who died from causes other than gastric carcinoma were censored for the survival analysis.

Histological evaluation

All surgical specimens were processed and examined according to the guideline of the Japanese Gastric Cancer Association[3]. Tumour location was classified as upper, middle or lower third of stomach. The diagnosis of carcinoma was based on the modified Vienna classification[16], and histological type determined according to the World Health Organization classification[17]. Differentiated tumours included well differentiated and moderately differentiated tubular adenocarcinoma, and papillary adenocarcinoma. Undifferentiated tumours included poorly differentiated tubular adenocarcinoma, signet ring cell carcinoma, mucinous adenocarcinoma, and other types. Depth of tumour invasion and lymph node involvement were determined according to the seventh edition of the AJCC staging manual[1].

Histological slides of the regional lymph nodes, as well as of the primary tumour when in the same slide as the lymph nodes, were split evenly and reviewed by two gastrointestinal pathologists. If a metastatic lymph node was suspected to have ENE, the two pathologists examined the specimen together and came to a consensus. ENE was defined as cancer cells infiltrating the extranodal adipose tissue beyond the capsule of the lymph node (*Fig. 1a*). Tumour cell nodules in perigastric fat tissue (not continuous with the primary tumour) without surrounding lymphoid tissue were also considered as involvement of lymph nodes with ENE (*Fig. 1b*). Tumour emboli in efferent or afferent lymphatic channels outside the lymph node capsule were not considered as ENE (*Fig. 1c*), nor was direct invasion of tumour into a lymph node (*Fig. 1d*). Lymphovascular invasion was present when tumour cells were identified in a tubular space lined by endothelial cells or inside a vascular wall structure. Perineural invasion was diagnosed when malignant cells were present in the perineural space of nerves. The tumour was considered as ENE-positive when one or more of the metastatic lymph nodes showed ENE.

Statistical analysis

SPSS® version 12·0 for Windows® (IBM, Armonk, New York, USA) was used for all statistical analyses. The χ^2 test was used to assess the association of ENE with sex, tumour location, depth of invasion, grade of differentiation, gross pattern and the presence of lymphovascular/perineural invasion. The Mann–Whitney *U* test was performed to compare age, tumour size, number of metastatic and harvested lymph nodes according to ENE. The disease-specific survival rate was determined by the Kaplan–Meier method, and the log rank test was used to compare groups according to T and N category. Univariable and multivariable Cox regression models were used to identify prognostic factors. Statistical significance was set at $P < 0{\cdot}050$.

Results

Some 4323 patients who underwent curative gastrectomy with lymphadenectomy for primary gastric carcinoma between January 2003 and June 2006 were selected from the database. A total of 1143 patients with positive lymph nodes were included in the study (*Fig. 2*). Patient demographics, T category and histopathological characteristics are shown in *Table 1*. Median age was 61 (range 24–90) years and 744 patients (65·1 per cent) were men. Mean(s.d.) numbers of metastatic lymph nodes, and removed nodes were 6·7(6·9) and 30·5(11·2) respectively. ENE in a metastatic lymph node was identified in 42·3 per cent of patients.

ENE was observed more frequently in men, and in larger tumours, Borrmann type 2 or 3 cancers, and tumours with deeper invasion of the gastric wall. It was also associated with increased number of metastatic lymph nodes, and the presence of lymphovascular and perineural invasion (*Table 1*).

Table 1 Clinicopathological characteristics of patients with node-positive gastric carcinoma with and without extranodal extension

	All patients ($n = 1143$)	ENE-positive ($n = 483$)	ENE-negative ($n = 660$)	P§
Age (years)*	61 (24–90)	61 (25–90)	60 (24–87)	0·246¶
Sex ratio (M : F)	744 : 399	337 : 146	407 : 253	0·005
ASA score*	2 (1–3)	2 (1–3)	2 (1–3)	0·775¶
Co-morbidity				0·522
None	727 (63·6)	302 (62·5)	425 (64·4)	
Single disease	315 (27·6)	133 (27·5)	182 (27·6)	
Multiple diseases	101 (8·8)	48 (9·9)	53 (8·0)	
Tumour location in stomach				0·137
Lower	657 (57·5)	282 (58·4)	375 (56·8)	
Middle	255 (22·3)	93 (19·3)	162 (24·5)	
Upper	190 (16·6)	89 (18·4)	101 (15·3)	
Entire stomach	41 (3·6)	19 (3·9)	22 (3·3)	
Tumour size (cm)†	6·5(3·3)	7·0(3·2)	6·2(3·3)	< 0·001¶
Gross appearance‡				< 0·001
I	17 (1·5)	4 (0·8)	13 (2·0)	
IIa/IIb/IIc	129 (11·3)	15 (3·1)	114 (17·3)	
III	17 (1·5)	2 (0·4)	15 (2·3)	
B1	13 (1·1)	3 (0·6)	10 (1·5)	
B2/B3	894 (78·2)	431 (89·2)	463 (70·2)	
B4/B5	73 (6·4)	28 (5·8)	45 (6·8)	
Differentiated				0·371
Yes	352 (30·8)	156 (32·3)	196 (29·7)	
No	791 (69·2)	327 (67·7)	464 (70·3)	
Laurén classification				0·096
Intestinal	409 (35·8)	198 (41·0)	211 (32·0)	
Diffuse	514 (45·0)	197 (40·8)	317 (48·0)	
Mixed	152 (13·3)	58 (12·0)	94 (14·2)	
Unknown	68 (5·9)	30 (6·2)	38 (5·8)	
pT category				< 0·001
T1	163 (14·3)	22 (4·6)	141 (21·4)	
T2	187 (16·4)	42 (8·7)	145 (22·0)	
T3	450 (39·4)	222 (46·0)	228 (34·5)	
T4a	332 (29·0)	190 (39·3)	142 (21·5)	
T4b	11 (1·0)	7 (1·4)	4 (0·6)	
No. of metastatic LNs†	6·7(6·9)	9·8(7·4)	4·4(5·5)	< 0·001¶
No. of removed LNs†	30·5(11·2)	31·1(11·0)	30·1(11·3)	0·099¶
N category				< 0·001
N1	390 (34·1)	69 (14·3)	321 (48·6)	
N2	340 (29·7)	131 (27·1)	209 (31·7)	
N3a	295 (25·8)	192 (39·8)	103 (15·6)	
N3b	118 (10·3)	91 (18·8)	27 (4·1)	
Lymphovascular invasion				< 0·001
Yes	718 (62·8)	348 (72·0)	370 (56·1)	
No	425 (37·2)	135 (28·0)	290 (43·9)	
Perineural invasion				< 0·001
Yes	433 (37·9)	229 (47·4)	204 (30·9)	
No	562 (49·2)	189 (39·1)	373 (56·5)	
Unknown	148 (12·9)	65 (13·5)	83 (12·6)	
Adjuvant chemotherapy				< 0·001
Yes	1038 (90·8)	460 (95·2)	578 (87·6)	
No	105 (9·2)	23 (4·8)	82 (12·4)	

Values in parentheses are percentages unless indicated otherwise; values are *median (range) and †mean(s.d.). ‡The gross appearance of early gastric cancer was classified into types I (protruded), II (superficial: a, elevated; b, flat; c, depressed) and III (excavated) according to the classification of the Japanese Gastric Cancer Association, and that of advanced gastric cancer was categorized based on the Borrmann classification (B1, polypoid; B2, ulcerofungating; B3, ulceroinfiltrating; B4, diffuse infiltrating; B5, unclassifiable). ENE, extranodal extension; ASA, American Society of Anesthesiologists; LN, lymph node. §χ^2 test, except ¶Mann–Whitney U test.

Table 2 Univariable and multivariable Cox regression analysis of prognostic factors for disease-specific survival in patients with node-positive gastric carcinoma

	Univariable analysis		Multivariable analysis	
	Hazard ratio	*P*	Hazard ratio	*P*
Sex		0·014		
F	1·00 (reference)			
M	1·31 (1·06, 1·62)			
T category		< 0·001		< 0·001
T1	1·00 (reference)		1·00 (reference)	
T2	2·91 (1·43, 5·91)		2·06 (0·95, 4·47)	
T3	7·00 (3·70, 13·26)		3·87 (1·93, 7·74)	
T4	13·23 (7·01, 24·99)		5·23 (2·59, 10·56)	
N category		< 0·001		< 0·001
N1	1·00 (reference)		1·00 (reference)	
N2	2·12 (1·53, 2·92)		1·60 (1·12, 2·30)	
N3a	4·86 (3·60, 6·55)		2·37 (1·66, 3·40)	
N3b	7·40 (5·29, 10·35)		3·00 (1·98, 4·55)	
Extranodal extension		< 0·001		0·001
No	1·00 (reference)		1·00 (reference)	
Yes	2·95 (2·41, 3·61)		1·52 (1·19, 1·96)	
Lymphovascular invasion		< 0·001		0·003
No	1·00 (reference)		1·00 (reference)	
Yes	2·08 (1·66. 2·62)		1·52 (1·16, 1·98)	
Perineural invasion		< 0·001		0·031
No	1·00 (reference)		1·00 (reference)	
Yes	2·34 (1·89, 2·90)		1·30 (1·02, 1·65)	
Laurén classification		0·016		
Intestinal	1·00 (reference)			
Diffuse	1·36 (1·09, 1·71)			
Mixed	1·05 (0·76, 1·46)			

Values in parentheses are 95 per cent c.i.

Prognostic factors for lymph node-positive gastric carcinoma

Univariable analysis revealed that male sex, advanced T and N category, the presence of ENE in metastatic lymph nodes, lymphovascular and/or perineural invasion, and diffuse-type histology were associated with a poor prognosis in node-positive gastric carcinoma. In multivariable analysis, T category, N category, ENE, lymphovascular invasion and perineural invasion remained as independent prognostic factors for disease-specific survival (*Table 2*).

Disease-specific survival according to extranodal extension

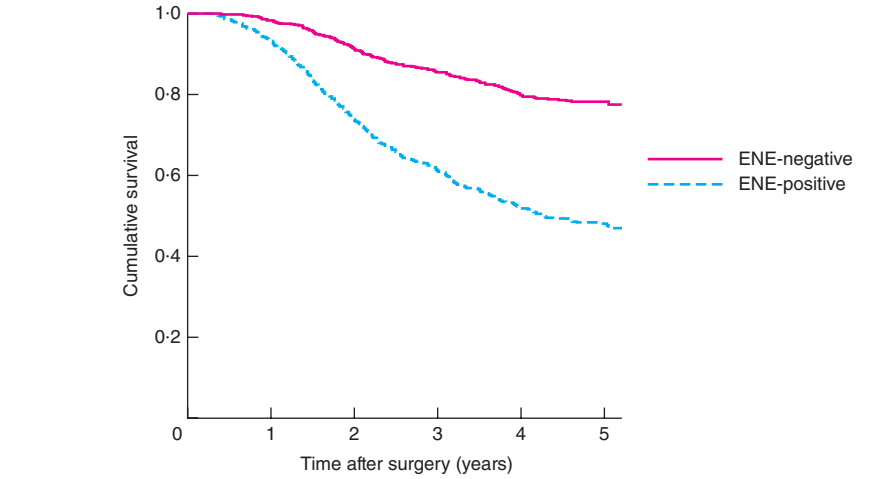
Median follow-up was 60·9 (range 1·4–84) months, and did not differ for patients with and those without ENE. The 5-year survival rate of patients with ENE-positive tumours was lower than that in patients with ENE-negative tumours: 48·1 *versus* 78·2 per cent respectively ($P < 0·001$) (*Fig. 3a*). This was true for all T and N categories ($P < 0·001$) (*Fig. 3b,c*).

Prognostic significance of extranodal extension in early gastric cancer

To investigate the prognostic significance of ENE in early gastric cancer, a subgroup analysis was performed of 163 patients with T1 tumours. Age, sex, tumour location and number of lymph nodes in this group were similar to values in the study population. Tumour size, number of metastatic lymph nodes, and prevalence of lymphovascular and perineural invasion were lower (*Table S1*, supporting information).

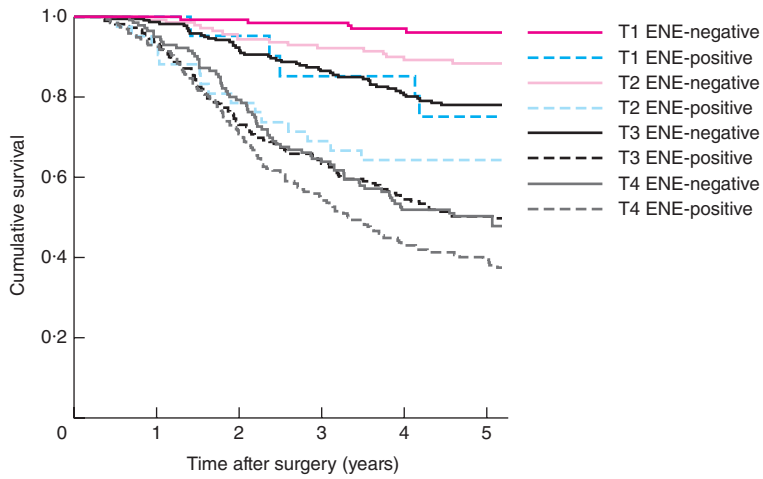
Twenty-two patients (13·5 per cent) had ENE-positive tumours, and ENE was the only indicator of poor prognosis (*Table 3*). Disease-specific 5-year survival rates for ENE-positive and ENE-negative patients were 75 and

96·9 per cent respectively ($P < 0·001$). To eliminate the possible effect of adjuvant chemotherapy in patients with early gastric cancer on survival, 63 patients who did not receive chemotherapy after gastrectomy were analysed separately. ENE maintained its prognostic significance for disease-specific survival: 86 *versus* 100 per cent for patients with ENE-positive and ENE-negative tumours respectively ($P = 0·007$).



No. at risk						
ENE-negative	660	641	583	531	463	397
ENE-positive	483	448	345	276	223	177

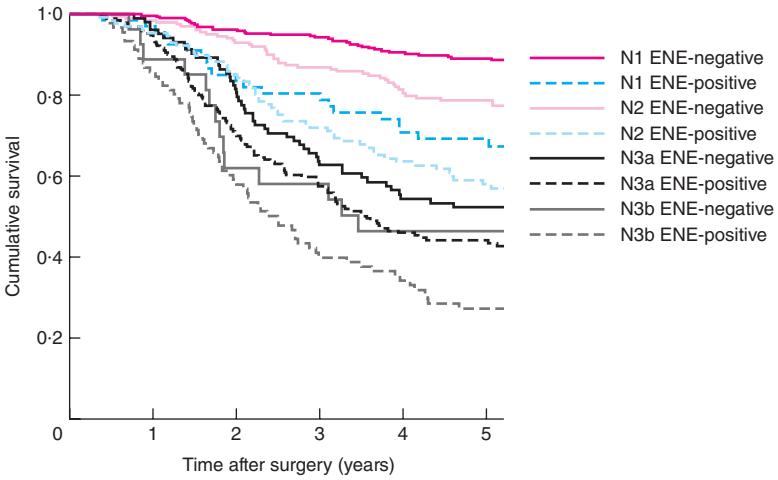
a Overall survival



No. at risk						
T1 ENE-negative	141	140	136	130	117	92
T1 ENE-positive	22	21	19	17	17	12
T2 ENE-negative	145	143	133	128	116	101
T2 ENE-positive	42	39	33	29	26	21
T3 ENE-negative	228	222	204	185	161	140
T3 ENE-positive	222	206	155	130	107	86
T4 ENE-negative	146	135	109	87	68	63
T4 ENE-positive	197	183	139	101	74	59

b Survival according to T category

Fig. 3 Survival in patients with node-positive gastric adenocarcinoma: **a** overall survival, **b** survival according to T category and **c** survival according to N category in patients with and without extranodal extension (ENE). **a–c** $P < 0·001$ (log rank test)



No. at risk

N1 ENE-negative	321	318	300	286	253	218
N1 ENE-positive	69	66	55	51	44	36
N2 ENE-negative	209	200	184	167	147	123
N2 ENE-positive	131	123	105	87	73	58
N3a ENE-negative	103	99	83	63	52	45
N3a ENE-positive	192	181	132	103	76	64
N3b ENE-negative	27	24	16	15	11	11
N3b ENE-positive	91	78	53	35	30	19

C Survival according to N category

Fig. 3 Continued

Table 3 Multivariable Cox regression analysis of prognostic factors for disease-specific survival in patients with node-positive early gastric cancer

		Disease-specific survival	
	No. of patients* ($n = 163$)	Hazard ratio†	*P*
Extranodal extension			< 0·001
No	22 (13·5)	1·00 (reference)	
Yes	141 (86·5)	8·72 (2·34, 32·50)	
T category			0·561
T1a	25 (15·3)	1·00 (reference)	
T1b	138 (84·7)	1·93 (0·36, 10·42)	
N category			0·284
N1–N2	153 (93·9)	1·00 (reference)	
N3	10 (6·1)	2·30 (0·22, 23·74)	
Lymphovascular invasion			0·130
No	79 (48·5)	1·00 (reference)	
Yes	84 (51·5)	3·99 (0·46, 34·54)	
Perineural invasion			0·631
No	137 of 145 (94·5)	1·00 (reference)	
Yes	8 of 145 (5·5)	1·57 (0·32, 7·24)	
Adjuvant chemotherapy			0·140
Yes	99 (60·7)	1·00 (reference)	
No	64 (39·3)	3·10 (0·33, 29·11)	

Values in parentheses are *percentages and †95 per cent c.i.

Discussion

This study shows that ENE is associated with advanced T and N category, larger tumour size and lymphovascular/perineural invasion. This is in agreement with other studies[12,14] showing that ENE is related closely to tumour aggressiveness. The association with male sex may be due to the fact that more men had tumours of advanced stage. Only lymph node-positive gastric cancers were included in the present study to clarify the prognostic significance of

ENE. All previous studies on ENE in gastric carcinoma included node-negative patients, and the actual numbers of node-positive cases with ENE were much lower than in the present study[12,14].

The presence of ENE was an independent prognostic predictor in multivariable analysis. Tumours with ENE of every T and N category were associated with poorer survival rates than those without ENE. Interestingly, patients with T1 or N1 tumours with ENE were found to have a worse prognosis than those with T2 or N2 tumours without ENE; this loss of homogeneity within the same T or N category occurred for all T and N categories. Therefore, detailed pathological examination to determine the presence of ENE should be performed.

Other studies[12–15] have reported on the prognostic significance of tumour cells identified beyond the capsule of metastatic lymph nodes in gastric cancer. Some studies[12,14] concentrated on infiltration of cancer cells beyond the nodal capsule, which was defined as ENE. Other studies[13,15] focused on the presence of tumour cells in extramural tissue discontinuous with either the primary lesion or locoregional lymph nodes, defined as tumour deposits. In colorectal cancer, the seventh edition of the AJCC staging system[1] categorizes pericolic or perirectal tumour metastasis as lymph node metastasis or tumour deposits, depending on the presence of surrounding lymph node tissues. However, in gastric cancer, all perigastric metastatic nodules are considered to be regional lymph node metastasis regardless of surrounding lymphoid tissue[1]. The present study followed the guidelines of the AJCC and considered tumour deposits to be ENE. A recent Korean study[18] reported that neither shape nor size could establish the true origin of perigastric tumour deposits, and morphological subclassification is also insufficient to distinguish between lymph node metastasis and other types of invasion such as vascular or neural invasion.

Despite excellent oncological outcomes, a significant number of patients with early gastric cancer still experience recurrence, but the role of adjuvant treatment for pT1 N1 and pT1 N2 tumours has not been established. This study showed that groups with pT1 N1, pT1 N2 and pT1 N3 disease had 5-year survival rates of 93·7, 91·5 and 90·0 per cent respectively, similar to findings from other studies focusing on node-positive early gastric cancer[19,20]. However, N category in itself was not a statistically significant prognostic factor, possibly owing to the scarcity of patients with pN3 disease. Rather, the present analysis demonstrated that ENE was the only prognostic factor in early cancers with lymph node metastasis. Although adjuvant chemotherapy has not been considered standard treatment for pT1 N1 and pT1 N2 tumours because of perceived low recurrence rates, based on the present observation patients with early gastric cancer showing ENE might be candidates for adjuvant treatment in future clinical trials.

The limitations of this study are its retrospective design and that patients were treated in a single institution, restricting the study's generalizability. However, it is the first report to suggest that ENE is an independent prognostic factor for early gastric cancer. In addition, the inclusion of tumour deposits as ENE would be useful in clinical practice according to the current AJCC guideline[1].

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References

1 Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol* 2010; **17**: 1471–1474.
2 Sakuramoto S, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A *et al.* Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. *N Engl J Med* 2007; **357**: 1810–1820.
3 Japanese Gastric Cancer Association. Japanese Classification of Gastric Carcinoma – 2nd English Edition. *Gastric Cancer* 1998; **1**: 10–24.
4 Lee SY, Hwang I, Park YS, Gardner J, Ro JY. Metastatic lymph node ratio in advanced gastric carcinoma: a better prognostic factor than number of metastatic lymph nodes? *Int J Oncol* 2010; **36**: 1461–1467.
5 Dhar DK, Kubota H, Kinukawa N, Maruyama R, Kyriazanos ID, Ohno S *et al.* Prognostic significance of metastatic lymph node size in patients with gastric cancer. *Br J Surg* 2003; **90**: 1522–1530.
6 Bhayani MK, Yener M, El-Naggar A, Garden A, Hanna EY, Weber RS *et al.* Prognosis and risk factors for early-stage adenoid cystic carcinoma of the major salivary glands. *Cancer* 2012; **118**: 2872–2878.
7 Shaw RJ, Lowe D, Woolgar JA, Brown JS, Vaughan ED, Evans C *et al.* Extracapsular spread in oral squamous cell carcinoma. *Head Neck* 2010; **32**: 714–722.
8 Fajkovic H, Cha EK, Jeldres C, Robinson BD, Rink M, Xylinas E *et al.* Extranodal extension is a powerful prognostic factor in bladder cancer patients with lymph node metastasis. *Eur Urol* 2013; **64**: 837–845.
9 Randolph G, Duh QY, Heller KS, Livolsi VA, Mandel SJ, Steward D *et al.* The prognostic significance of nodal metastases from papillary thyroid carcinoma can be stratified

based on the size and number of metastatic lymph nodes, as well as the presence of extranodal extension. ATA Surgical Affairs Committee's Taskforce on Thyroid Cancer Nodal Surgery. *Thyroid* 2012; [Epub ahead of print].
10 Mignano JE, Zahurak ML, Chakravarthy A, Piantadosi S, Dooley WC, Gage I. Significance of axillary lymph node extranodal soft tissue extension and indications for postmastectomy irradiation. *Cancer* 1999; **86**: 1258–1262.
11 Yamashita H, Noguchi S, Murakami N, Kawamoto H, Watanabe S. Extracapsular invasion of lymph node metastasis is an indicator of distant metastasis and poor prognosis in patients with thyroid papillary carcinoma. *Cancer* 1997; **80**: 2268–2272.
12 Choi WH, Kim S, Shen J, Cheong JH, Hyung WJ, Kim YI *et al.* Prognostic significance of perinodal extension in gastric cancer. *J Surg Oncol* 2007; **95**: 540–545.
13 Etoh T, Sasako M, Ishikawa K, Katai H, Sano T, Shimoda T. Extranodal metastasis is an indicator of poor prognosis in patients with gastric carcinoma. *Br J Surg* 2006; **93**: 369–373.
14 Nakamura K, Ozaki N, Yamada T, Hata T, Sugimoto S, Hikino H *et al.* Evaluation of prognostic significance in extracapsular spread of lymph node metastasis in patients with gastric cancer. *Surgery* 2005; **137**: 511–517.
15 Koike H, Ichikawa D, Kitamura K, Tsuchihashi Y, Yamagishi H. Perinodal involvement of cancer cells in gastric cancer patients. *Surgery* 2004; **135**: 266–272.
16 Schlemper RJ, Riddell RH, Kato Y, Borchard F, Cooper HS, Dawsey SM *et al.* The Vienna classification of gastrointestinal epithelial neoplasia. *Gut* 2000; **47**: 251–255.
17 Flejou JF. [WHO classification of digestive tumors: the fourth edition.] *Ann Pathol* 2011; **31**(Suppl): S27–S31.
18 Lee HS, Lee HE, Yang HK, Kim WH. Perigastric tumor deposits in primary gastric cancer: implications for patient prognosis and staging. *Ann Surg Oncol* 2013; **20**: 1604–1613.
19 Cheong JH, Hyung WJ, Shen JG, Song C, Kim J, Choi SH *et al.* The N ratio predicts recurrence and poor prognosis in patients with node-positive early gastric cancer. *Ann Surg Oncol* 2006; **13**: 377–385.
20 Saka M, Katai H, Fukagawa T, Nijjar R, Sano T. Recurrence in early gastric cancer with lymph node metastasis. *Gastric Cancer* 2008; **11**: 214–218.

Supporting information

Additional supporting information may be found in the online version of this article:

Table S1 Clinicopathological characteristics and prognostic factors in patients with node-positive T1 gastric carcinoma (Word document)