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Node-extranodal soft tissue stage based on extranodal metastasis is associated with poor prognosis of patients with gastric cancer

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ABSTRACT

Background: The purpose of this study was to evaluate the effect of Node-Extranodal soft tissue (pNE) stage based on Extranodal Metastasis (EM) on recurrence and survival in patients with gastric cancer (GC).

Materials and methods: A total of 642 patients were divided into two groups according to statue of EM. Clinicopathologic features were compared among the two groups, the log-rank test was used to assess statistical differences between the groups. Independent prognostic factors were identified by the Cox proportional hazards regression model. According to the number of EMs, EM was incorporated into the pN stage of gastric carcinoma. The 5-y overall survival (OS) and disease free survival (DFS) rates were 48.1% and 17.4%, 44.5% and 14.3% between the two groups. Patients with EM had a deeper tumor invasion and more number of lymph node metastases. Peritoneal dissemination and distant metastasis were more frequent with EM. EM is an independent risk factor for distance recurrence (odds ratio = 1.605), and it is the highest risk factor for peritoneal recurrence (odds ratio = 2.448). Multivariate analysis showed that depth of tumor invasion ($P = 0.025$), lymph node metastasis ($P < 0.001$), and EM ($P = 0.006$) were independent factors associated with OS. Furthermore, EM ($P = 0.0039$) was also an independent prognostic factor for DFS. The differences in prognostic prediction between the seventh edition of the pN classification and the pNE classification were directly compared. We found the pNE classification (hazard ratio = 1.730, $P < 0.001$) was more appropriate for predicting the OS of GC patients after curative surgery, and the −2 loglikehood of the pNE staging (4533.991) is smaller than the value of pN.

Conclusions: EM was closely associated with cancer aggressiveness and the presence of EM was a significant independent predictor of reduced DFS and OS in GC patients. EM is an independent risk factor for distance recurrence, especially for peritoneal recurrence, the selection of postoperative adjuvant therapy in systemic (intravenous or intra-arterial) and regional (intraperitoneal) based on EM may be a reasonable approach. The lymph node imaging techniques such as injecting nanocarbon during surgery should be applied. As an

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important prognostic factor, EM should be incorporated into N stage according to its number retrieved in postoperative samples.

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1. Introduction

Lymph node metastasis is considered as the foremost important factor in determining the prognosis of Gastric Cancer (GC) patients undergoing curative resection [1]. Treatment guidelines for GC have been issued, and a standard therapeutic strategy by stage has been established [2]. Although gastrectomy with D2 lymph node dissection has been increasingly regarded as the standard surgical procedure for most patients with operable GC, the 5-y overall survival (OS) rate and disease free survival (DFS) rate are still poor [3,4]. Extranodal metastasis (EM), found in the extranodal soft tissue by histologic examination, was discontinuous with the primary lesion or the locoregional lymph nodes, which may exhibit spreading of cancer cells. And it is found during routine examination of about 10%–28% of resected gastric carcinoma specimen [5].The presence of EM has also been regarded as a prognostic factor in many other cancers [6–9].However, in dealing with GC patients with lymph node metastasis, rare attention has been paid to the prognostic value of the presence of EM [10]. The aim of this study is to assess the incidence and prognostic significance of EM in GC patients after curative resection. Then the study intends to explore the relationship between EM and patterns of recurrence and estimate the risk factors for recurrence. In addition, we classified them into several different categories based on the number of EMs, afterward we determined whether EM should be combined into N stage system.

2. Materials and methods

2.1. Patients and tissue samples

A total of 1750 patients with GC underwent surgery at Tianjin Medical University Cancer Institute and Hospital during January 2002–December 2007, whose data entered into a prospectively maintained database. Eligibility criteria included in this study were as follows: (1) gastric adenocarcinoma identified by histopathologic examination, (2) histologically confirmed R0 resection, (3) availability of complete follow-up data, (4) radical resection and D2 lymphadenectomy performed, and (5) patients whose number of lymph nodes retrieved were not <15. The exclusion criteria were as follows: (1) patients who underwent palliative surgery, (2) patients who had distant metastasis or peritoneal dissemination that was confirmed during the operation. Based on these criteria, 1108 patients out of 1750 were excluded for this study. Out of those excluded, 343 cases had <15 lymph nodes harvested for pathologic examination, 120 cases had undergone a palliative gastrectomy, 235 cases had D0 and D1 lymph node resection, 28 cases died within 1 mo after surgery, 83 cases had distant metastasis before the gastrectomy, 45 cases had peritoneal dissemination before gastrectomy, and 254 cases were lost to follow-up. Ultimately, 642 patients were included for the analysis. All resected specimens and dissected lymph nodes containing some amounts of surrounding fat tissues were fixed in 10% formalin, embedded in

Table 1 – Correlation between EM and clinicopathologic factors in gastric carcinoma patients following a curative resection.

Characteristics	EM		χ^2	P
	Negative ($n = 470$)	Positive ($n = 172$)		
Age (y)			4.643	0.031
< 65	269 (57.2)	82 (47.7)		
≥65	201 (42.8)	90 (52.3)		
Gender			0.337	0.562
Female	159 (33.8)	54 (31.4)		
Male	311 (66.2)	118 (68.6)		
Tumor location			10.127	0.018
Upper one-third	122 (26.0)	50 (29.1)		
Middle one-third	67 (14.3)	32 (18.6)		
Lower one-third	241 (51.3)	66 (38.4)		
2/3 or More	40 (8.5)	24 (14.0)		
Tumor size			15.817	<0.001
<5 cm	269 (57.2)	68 (39.5)		
≥5 cm	201 (42.8)	104 (60.5)		
Borrmann type			34.868	<0.001
I/II	207 (44.0)	32 (56.0)		
III/IV	263 (56.0)	140 (81.4)		
Histology			22.488	<0.001
Differentiated	143 (30.4)	20 (11.6)		
Undifferentiated	327 (69.6)	152 (88.4)		
Depth of invasion			25.368	<0.001
pT1	17 (3.6)	0 (0)		
pT2	56 (11.9)	2 (1.2)		
pT3	21 (4.5)	8 (4.7)		
pT4	376 (80.0)	162 (94.2)		
Lymph node metastasis			71.928	<0.001
pN0	157 (33.4)	18 (10.5)		
pN1	87 (18.5)	12 (7.0)		
pN2	95 (20.2)	38 (22.1)		
pN3	131 (27.9)	104 (60.5)		
Type of gastrectomy			9.434	0.002
Subtotal	353 (75.1)	108 (62.8)		
Total	117 (24.9)	64 (37.2)		
Peritoneal recurrence			31.066	<0.001
Yes	80 (17.0)	65 (37.8)		
No	390 (83.0)	107 (62.2)		
Locoregional recurrence			0.019	0.889
Yes	98 (20.9)	35 (20.3)		
No	372 (79.1)	137 (79.7)		
Distant recurrence			6.248	0.012
Yes	86 (18.3)	47 (27.3)		
No	384 (81.7)	125 (72.7)		

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