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*Original Article*

# Risk factors associated with splenic hilar lymph node metastasis in patients with advanced gastric cancer in northwest China

Zhenqiang Sun[1,2], Qisan Wang[1], Xianbo Yu[3], Chunlin Ou[2], Lizhong Yao[1], Kun Liu[1], Lin Liu[1], Lei Ge[1], Fa Fang[1], Zeliang Zhao[1], Haijiang Wang[1]

*[1]Department of Gastrointestinal Surgery, Affiliated Tumor Hospital, Xinjiang Medical University, Urumqi 830011, China; [2]Cancer Research Institute, Central South University, Changsha 410078, China; [3]Department of Gynaecology, Cangzhou People's Hospital, Cangzhou 061000, China*

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**Abstract:** There are plenty of risk factors associated with splenic hilar lymph node metastasis (SHLNM) in patients with advanced gastric cancer (AGC). Whereas, their main influencing factors have not reached a consensus yet. The aim of the study is to investigate the related clinicopathological factors influencing SHLNM in AGC. A retrospective study was performed to investigate 150 patients who underwent D2 curative partial or total gastrectomy for gastric carcinoma from January 2007 to November 2012. Clinicopathological factors were analyzed by univariate and multivariate analysis. A total of 10.7% (16/150) of the patients had SHLNM. The overall ratio of metastatic lymph node (positive lymph nodes/lymph nodes harvested) in the splenic hilum was 17.5% (38/217). Univariate analysis results showed SHLNM was related with depth of invasion, tumor grade, tumor size, tumor location and Bormann type, with significant difference ($P$<0.05); Multivariate analysis demonstrated that SHLNM was related with depth of invasion and tumor size, with significant difference ($P$<0.05). Consequently, depth of invasion, tumor grade, tumor size, tumor location and Bormann type were associated with SHLNM in AGC, meanwhile depth of invasion and tumor size are independent risk factors. Preoperative predicting risk factors of SHLNM greatly benefits making more rational surgical scheme of treating AGC.

**Keywords:** Advanced gastric cancer, splenic hilar lymph node, metastasis, risk factor

## Introduction

Gastric cancer, deriving from gastric mucosal epithelial cells, is one of the most common malignant tumors. The morbidity of gastric cancer in the world is 13.86 per 100000, meanwhile it presents high incidence in China. At present, the mortality of gastric cancer is still on the rise and it manifests a young trend. Hence, gastric cancer is one of the most common malignant tumors threatening human health [1]. Radical excision surgery is still the most main way to cure gastric cancer [2, 3]. However, postoperative recurrence rate of gastric cancer reaches to from 50% to 70%, which seriously affects therapeutic effect [4, 5]. The 5-year survival rate of advanced gastric cancer is only 30-40% [6]. Therefore, early discovery, early diagnosis and early efficient treatment become very meaningful.

The main metastatic way is through lymph node in advanced gastric cancers [7, 8]. Splenic hilum lymph nodes (also called No. 10) distribute along distal pancreas to splenic vessel, which is the second station lymph nodes (D2) that is necessarily removed by the curative partial or total gastrectomy for gastric cancer [9, 10]. Resecting splenic hilar lymph node in curative surgery easily injure spleen and vascular around [11-13]. Obviously, the above increase difficulty and risk of surgery in a certain degree [14]. Therefore, exploring risk factors associated with splenic hilar lymph node metastasis (SHLNM) of advanced gastric cancer is very significant [15]. In the study, a retrospective study was performed to investigate 150 patients who underwent D2 curative partial or total gastrectomy for the patients with advanced gastric cancers, and analyzed the association between clinicopathological features and SHLNM.

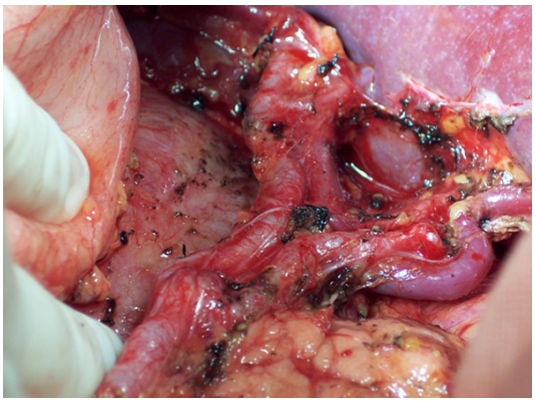

**Figure 1.** Skeletonized lymphadenectomy in hilus lienis during D2 lymphadenectomy for treating AGC patients.

## Materials and methods

### *Patients and specimens*

A total of 150 patients who underwent D2 curative partial or total gastrectomy for gastric carcinoma [16] from January 2007 to November 2012 were enrolled in this study. The patient population was composed of 118 males and 32 females with a median patient age of 57.5 years (range 37-78). Of the 150 cases, 72 were under 70 years age , and 78 were over 80 years old; 92 were Han Nationality, 42 were Uyghur Nationality and 16 were Kazak Nationality; in the Borrmann type, 58 were the type of ulcerative, 66 were mass and 26 were infiltrative; 84 were well-differentiated and moderately, meanwhile, 66 were poorly differentiated; 25 with diffuse infiltration, 56 with middle-superior carcinoma and 69 with inferior carcinoma; 49 were located at the lesser curvature, 45 were located at greater curvature and 56 were located at both curvatures; 89 were the distance from tumor margin to splenic hilum <5 cm, and 61 were the distance from tumor margin to splenic hilum ≥5 cm; in depth of invasion, 78 were the T2, 49 were the T3 and 23 were the T4; 63 with carcinoma cell embolus and 87 without.

### *Selection criterion*

Inclusion criteria were as followings: firstly, preoperative staging was confirmed by endoscopic ultrasound, pathological and computed tomography (CT) as the advanced gastric cancers; secondly, none of the patients before received preoperative chemotherapy and/or radiation therapy; thirdly, open surgery could reach D2 radical standard; fourthly, definite diagnosis was confirmed by postoperative pathological results as the advanced gastric cancer further; finally, splenic hilum lymph node was completely removed in intraoperative and postoperatively verified metastasis or not. Exclusion criteria were as followings: to begin with, clinical data of the patients was incomplete and unanalyzable; next, combined with other cancers; in addition, accompanied with other diseases which could induce lymphadenopathy and metastasis.

### *Follow-up assessments*

All patients above enrolled in our hospital were registrated, and complete personal follow-up files of the patients with explicit pathological diagnosis were established. After surgery, the patients were followed up once every three weeks within 6 moths, once every three months for two years, and then once every 6 months up to death or losing contact. Two follow-up ways were used, outpatient or inpatient review and telephone follow-up, including postoperative chemotherapy, postoperative radiotherapy, chemotherapy regimens, therapeutic course count, side effects, recurrence and survival time.

### *Statistical analysis*

All statistical analyses were carried out using SPSS for Windows, version 18.0 (SPSS Inc., Chicago, IL, United States). Univariate analysis was performed using chi-square test and the Fisher's exact test. Multivariate analysis was conducted using Logistic regression analysis. $P<0.05$ was considered to indicate a statistically significant difference.

## Results

### *Lymph node resection*

For the whole 150 patients, the total number of lymph node resection was 2658 with the mean of 17.7 per patient, of which the positive metastasis ratio was 28.7% (763/2658). A total of 10.7% (16/150) of the patients had SHLNM of AGC. The number of lymph node resection in splenic hilum was 217, of which 38 was positive metastasis. Skeletonized lymphadenectomy in

**Table 1.** Univariate analysis results between clinicopathological factors and splenic hilar lymph node metastasis (SHLNM)

| Parameters | n | SHLNM (%) | | $\chi^2$ | *P* value |
|---|---|---|---|---|---|
| | | Negative | Positive | | |
| Gender | | | | 0.492 | 0.483 |
| Male | 118 | 107 | 11 (9.3) | | |
| Female | 32 | 27 | 5 (15.6) | | |
| Age (year) | | | | 2.013 | 0.156 |
| <60 | 72 | 67 | 5 (6.9) | | |
| ≥60 | 78 | 67 | 11 (14.1) | | |
| Nationality | | | | 0.184 | 0.668 |
| Han | 92 | 83 | 9 (9.9) | | |
| Uyghur | 42 | 37 | 5 (11.9) | | |
| Kazak | 16 | 14 | 2 (12.5) | | |
| Borrmann type | | | | 5.556 | 0.018 |
| Ridgy/Locally Ulcerative | 58 | 57 | 1 (0.02) | | |
| Infiltrative Ulcerative | 66 | 55 | 11 (0.17) | | |
| Infiltrative | 26 | 22 | 4 (0.15) | | |
| Differentiation degree | | | | 4.453 | 0.035 |
| Well/Moderately | 84 | 79 | 5 (6.0) | | |
| Poorly | 66 | 55 | 11 (16.7) | | |
| Lengthwise position | | | | 7.608 | 0.006 |
| Suffuse infiltration | 25 | 22 | 3 (12.0) | | |
| Mid-upper | 56 | 43 | 13 (23.2) | | |
| Lower | 69 | 69 | 0 | | |
| Lateral location | | | | 4.586 | 0.032 |
| Lesser curvature | 49 | 47 | 2 (4.1) | | |
| Greater curvature | 45 | 37 | 8 (17.8) | | |
| Complete cycle | 56 | 50 | 6 (10.7) | | |
| Tumor size (cm) | | | | 12.225 | 0.001 |
| <5 | 89 | 86 | 3 (3.4) | | |
| ≥5 | 61 | 48 | 13 (21.3) | | |
| Depth of invasion | | | | 21.350 | 0.001 |
| T2 | 78 | 77 | 1 (1.3) | | |
| T3 | 49 | 42 | 7 (14.3) | | |
| T4 | 23 | 15 | 8 (34.8) | | |
| Vascular tumor bolt | | | | 3.090 | 0.079 |
| Yes | 63 | 53 | 10 (15.9) | | |
| No | 87 | 81 | 6 (6.9) | | |

hilus lienis during D2 lymphadenectomy was carried out for treating some AGC patients (**Figure 1**).

*Univariate analysis results*

For all the patients, univariate analysis manifested that SHLNM of AGC was closely associated with Borrmann type, differentiation degree, tumor lengthwise position, tumor lateral location, tumor size and depth of invasion (P<0.05 for all parameters); In other words, infiltrative type, poorer differentiation degree, mid-upper, greater curvature, the larger size and deeper invasion AGC more easily occurs SHLNM. SHLNM of AGC was not correlated with age, gender, nationality and vascular tumor bolt (P>0.05 for all parameters) (**Table 1**).

*Multivariate analysis results*

For these 150 patients, logistic regression analysis showed that SHLNM of AGC had close correlation with tumor size and depth of invasion, which suggested that these two parameters should be independent risk factors of SHLNM of AGC (**Table 2**). That is to say, the larger the tumor size is, the higher probability SHLNM will occur; the deeper the tumor invades, the easier SHLNM comes up.

## Discussion

Splenic hilar lymph node metastasis (SHLNM) of AGC status can influence the choice of surgical scheme, the judgment of metastasis of its downstream lymph node and the postoperative living quality [17, 18]. There are numerous potential risk factors associated with SHLNM of AGC and these potential risk factors may interact with each other [19, 20]. Therefore, it is of much difficulty to reveal clinicopathological features related with SHLNM of AGC by excluding plenty of other disturbing factors [21]. Some researchers reported that the SHLNM rate of AGC was 9.8%-18.3% [22, 23]. In our study, the SHLNM rate of AGC was 10.7%. Zhang [24] revealed that SHLNM had the relationship with age, tumor location, tumor size, depth of invasion, degree of radical surgery and lymphatic metastasis in No. 7, No. 9 and No. 4 sb by analyzing

**Table 2.** Multivariate analysis results between clinicopathological factors and splenic hilar lymph node metastasis (SHLNM)

| Clinicopathological index | Regression coefficient | Standard error | Wald | *P* value | OR | 95% CI |
|---|---|---|---|---|---|---|
| Depth of invasion* | | | | | | |
| T2 | | | 6.214 | 0.045 | | |
| T3 (1) | 2.650 | 1.269 | 4.360 | 0.037 | 14.148 | 1.177-170.130 |
| T4 (2) | 3.171 | 1.284 | 6.094 | 0.014 | 23.827 | 1.922-295.389 |
| Tumor size | 2.160 | 0.860 | 6.314 | 0.012 | 8.674 | 1.609-46.779 |

*Depth of invasion is an introduced dummy variable to produce the multivariate analysis. T2 is the internal reference.

the clinicopathological features of 590 patients with AGC. Furthermore, the features of age, tumor size, depth of invasion and lymph node metastasis in No. 4 sb were independent risk factors in AGC patients with SHLNM. In our study, SHLNM of AGC was closely associated with Borrmann type, differentiation degree, tumor lengthwise position, tumor lateral location, tumor size and depth of invasion. Multivariate analysis indicated that tumor size and depth of invasion were independent risk factors of SHLNM of AGC.

To date, the association between differentiation degree and SHLNM still remains controversial, but majority of researchers believe the two existed close correlation [25]. Differentiation degree had negative correlation with SHLNM of AGC [26, 27]. In detail, the poorer differentiation degree was, the lower SHLNM would be. Our study showed that the rate of SHLNM in the group with well/moderately differentiation (6%) was lower than that in the group with poor differentiation (16.7%). There were different explanations to this. Xue [28] reported that the gastric cancer cells more with poorer differentiation easily produce collagenase type IV that promoted the degradation of basement membrane and caused high rate SHLNM of AGC. However, Wu [29] explained that the rate of SHLNM was correlated with Matrix Metalloproteinase3 (MMP-3) expression induced by poorer differentiation of AGC. In addition, in the present study showed that SHLNM was associated with Borrmann type. The SHLNM rate of AGC with the ridgy/locally ulcerative, the infiltrative ulcerative and the infiltrative were 2%, 17% and 15% respectively. Some other studies reported that lymphatic metastasis more easily occurred in the infiltrative AGC compared with the local AGC, maybe because of tumor differentiation degree and growth pattern [30, 31]. Consequently, for well/moderately differentiation of AGC, the lower differentiation should be mainly chosen as a standard of removing lymph nodes and for poor differentiation of AGC, SHLNM should be manly selected as a criterion of lymph node resection for maximum benefit of AGC patients [32].

It is worth to note that SHLNM may be influenced by tumor location. In recent years, the incidence of gastric cancer in the upper third of the stomach showed an increasing tendency, and clinical symptoms presented late [33-35]. In addition, SHLNM easily happened in advanced upper third gastric cancer compared with some gastric cancers in the other location. SHLNM rate of advanced upper third gastric cancer ranged from 9.8% to 20.9% [36, 37]. In our study, SHLNM rate of mid-upper third gastric cancer was 23.2%, which was higher than the lower gastric cancer (0%). The conclusion was similar with Ikeguchi's previous reports [38]. What's more, our study demonstrated that the SHLNM rate of AGC locating at the greater curvature was 17.8%, higher than that at the lesser curvature. Meanwhile, Kusan [39] revealed that the SHLNM rate of AGC locating at the greater curvature was 17.0%, higher than that at the greater curvature (10%). The results suggested that SHLNM easily occurs in the gastric cancer at the greater curvature. Obviously, tumor location may be a predictor for SHLNM of AGC.

As is know to us, depth of invasion and tumor size can predict tumor staging in a certain degree. Some studies reported that the two above were potential factors influencing SHLNM [40, 41]. In our study, the SHLNM rate of AGC in tumor size equal or larger than 5 cm was 21.3%, higher than that in tumor size less than 5 cm (3.4%). This may be due to the fact that as the length of tumor size increase, the contact area of cancer cells with gastric submucosal

lymphatic vessel will gradually broaden [42], which caused higher SHLNM rate of AGC. Moreover, our study clarified that the SHLNM rate of AGC with staging T2 was 1.3%, much lower than that with staging T4 (34.8%). This result suggested that with increasing T staging, the SHLNM rate of AGC correspondingly would rise up, which was consistent with Zhang' report [24]. The reason may be that lymphatic capillaries in all layers of gastric wall converge into submucosal lymphatic vessels. Once tumor cells infiltrate into serous layer, the rate of lymph node metastasis will remarkably increase [43]. Consequently, the depth of invasion and tumor size of AGC are significant considerable factors to make the surgical scheme containing lymphadenectomy of hilus lienis.

In conclusion, there were really some risk factors associated with SHLNM of AGC, including depth of invasion, tumor grade, tumor size, tumor location and Bormann type, especially depth of invasion and tumor size as independent risk factors. Preoperatively forecasting the risk factors of SHLNM is very beneficial to make more reasonable surgical scheme and improve therapeutic effect for the patients with AGC [44].

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## Disclosure of conflict of interest

None.

**Address correspondence to:** Dr. Haijiang Wang, Department of Gastrointestinal Surgery, Affiliated Tumor Hospital, Xinjiang Medical University, 789 Suzhou Eeast Street, Urumqi 830011, China. Tel: +86-991-7819106; Fax: +86-991-7819106; E-mail: wanghaijiang0129@163.com

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