

RESEARCH ARTICLE

Risk of Lymph Node Metastases from Early Gastric Cancer in Relation to Depth of Invasion: Experience in a Single Institution

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Abstract

Background: An accurate assessment of potential lymph node metastasis is important for the appropriate treatment of early gastric cancers. Therefore, this study analyzed predictive factors associated with lymph node metastasis and identified differences between mucosal and submucosal gastric cancers. **Materials and Methods:** A total of 518 early gastric cancer patients who underwent radical gastrectomy were reviewed in this study. Clinicopathological features were analyzed to identify predictive factors for lymph node metastasis. **Results:** The rate of lymph node metastasis in early gastric cancer was 15.3% overall, 3.3% for mucosal cancer, and 23.5% for submucosal cancer. Using univariate analysis, risk factors for lymph node metastasis were identified as tumor location, tumor size, depth of tumor invasion, histological type and lymphovascular invasion. Multivariate analysis revealed that tumor size >2 cm, submucosal invasion, undifferentiated tumors and lymphovascular invasion were independent risk factors for lymph node metastasis. When the carcinomas were confined to the mucosal layer, tumor size showed a significant correlation with lymph node metastasis. On the other hand, histological type and lymphovascular invasion were associated with lymph node metastasis in submucosal carcinomas. **Conclusions:** Tumor size >2 cm, submucosal tumor, undifferentiated tumor and lymphovascular invasion are predictive factors for lymph node metastasis in early gastric cancer. Risk factors are quite different depending on depth of tumor invasion. Endoscopic treatment might be possible in highly selective cases.

Keywords: Early gastric cancer - lymph node metastasis - endoscopic treatment - depth of tumor invasion

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Introduction

In 1962, the Japanese Society of Gastroenterological Endoscopy defined early gastric cancer as a lesion confined to the mucosa and/or submucosa, regardless of lymph node metastatic status (Murakami et al., 1971). The need to define this category of gastric cancer is related to the difference in prognosis between early and advanced gastric cancer. The prognosis is generally favorable in early gastric cancers after radical surgery, with a 5-year survival rate of more than 90% (Hyung et al., 2002; Kwee et al., 2008). The proportion of early gastric cancer among all gastric cancers has increased to nearly 50% in Japan and Korea (Chang et al., 2012; Tatematsu et al., 2013). With more widespread mass screenings, as well as advances in endoscopic techniques and equipment, similar trends have been observed during the past few decades in China.

Many investigations have shown that the presence of lymph node metastasis is the most important prognostic factor for patients with early gastric cancer and has a significant influence on the selection of possible treatment (Ohta et al., 1987; Haves et al., 1996). Although radical

gastrectomy including lymph node dissection has been recognized as the standard surgical operation for early gastric cancer, unnecessary surgery could be avoided and endoscopic treatment might be a consideration in patients with early gastric cancer with negligible risk of lymph node metastasis. A lot of retrospective studies on early gastric cancer have established an indication for endoscopic treatment without lymph node dissection. However, the feasibility of endoscopic treatment for early gastric cancer is still in debate.

The present retrospective study was designed to evaluate the factors that can be predicted the presence of lymph node metastasis and to identify the difference between mucosal and submucosal gastric cancers in point of lymph node metastasis. Using these predictive factors, we established suitable criteria to elucidate which subgroup of early gastric cancer patients could be treated with endoscopic treatment instead of radical surgery.

Materials and Methods

This study enrolled 518 early gastric cancer

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patients, those were pathologically proven after curative gastrectomy with lymph node dissection from January 1994 to December 2008 at the Department of Abdominal Surgical Oncology, Cancer Hospital of the Chinese Academy of Medical Sciences, Peking Union Medical College.

All patients underwent radical subtotal or total gastrectomies, depending on the tumor location and intraoperative verification of tumor-free resection margins, as well as D2 or D1 lymphadenectomies. No patient has received neoadjuvant therapy before surgery. The methods of reconstruction after distal gastrectomy include Billroth I, II or Roux-en-Y. Roux-en-Y reconstruction and jejunal interposition are the most common methods used after a total gastrectomy.

The patients' clinical characteristics and histopathological parameters were analyzed. Clinicopathological factors, such as gender, age, tumor size, tumor location, macroscopic appearance, histological type, depth of tumor invasion, lymphovascular invasion and lymph node status, were defined according to the General Rules of the Japanese Classification of Gastric Carcinoma (2nd English edition) (Japanese Gastric Cancer Association Association, 1998). The maximum diameter of tumor was recorded as tumor size. Macroscopic type included elevated (I, protruded; IIa, superficial elevated), flat (IIb, superficial flat), depressed (IIc, superficial depressed; III, excavated) and mixed (depressed plus elevated). Tumor histology was classified into two groups: 1) differentiated, which included papillary adenocarcinoma and well or moderately differentiated adenocarcinoma; and 2) undifferentiated, which included poorly or undifferentiated adenocarcinoma, signet ring cell carcinoma and mucinous carcinoma. The depth of tumor invasion was classified as mucosa and submucosa carcinoma. Lymphovascular invasion was defined as the presence of tumor emboli either in the lymphatic duct or the vascular lumen.

Statistical analysis

Univariate and multivariate analyses of risk factors associated with lymph node metastasis were performed using the χ^2 test and logistic regression models, respectively. $p<0.05$ was considered statistically significant. Statistical analyses were performed with SPSS software, version 13.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

The study involved 349 men and 169 women, with a male:female ratio of 2.07:1. The median age of the enrolled patients was 58 years (24-82 years). Of the 518 patients, metastatic lymph node involvement was present in 79 (15.3%). The mucosal form of cancer presented with lymph node involvement in 3.3% of cases, in contrast to 23.5% of cases that were associated with submucosal forms. A total of 375 patients had tumors located in the lower third of the stomach. Eighty-four had tumors in the middle third of the stomach, while 59 had tumors in the upper third. Two hundred and seventy six cases had

tumors larger than 2cm in diameters, while 174 cases had tumors of 1.0-2cm, and 68 cases were less than 1.0cm. Tumor invasion was limited to the mucosal layer in 212 patients, while in 306 patients, the tumors had invaded the submucosal layer. Depressed-type tumors were macroscopically observed in 273 patients, flat-type tumors were observed in 188 patients, and elevated-type or mixed-type tumors were observed in the remaining 57 patients. Nearly two-thirds of the tumors were poorly differentiated. There were 18 cases of lymphovascular invasion.

The univariate analysis of factors predicting lymph node metastasis is presented in Table 1. Tumor location, tumor size, depth of tumor invasion, histological type and lymphovascular invasion were significantly correlated with lymph node metastasis. There was no significant difference in gender, age, macroscopic type. The multivariate analysis revealed that tumor size greater than 2.0 cm, submucosal invasion, poor tumor differentiation and lymphovascular invasion were independent risk factors associated with lymph node metastasis (Table 2). When the carcinomas were confined to the mucosal

Table 1. Risk Factors for Lymph Node Metastasis by Univariate Analysis

Factor	n	Lymph node metastasis (%)	χ^2	P-value
Gender				
Male	349	48 (13.8)	1.856	0.173
Female	169	31 (18.3)		
Age (years)				
≤60	336	52 (15.5)	0.038	0.846
>60	182	27 (14.8)		
Tumor Location				
Upper	59	3 (5.1)	16.393	0.001
Middle	84	4 (4.8)		
Lower	375	72 (19.2)		
Tumor Size(cm)				
<1.0	68	2 (2.9)	11.02	0.004
1.0-2.0	174	15 (8.6)		
>2.0	276	62 (22.4)		
Depth of Invasion				
Mucosal	212	7 (3.3)	32.847	0.001
Submucosal	306	72 (23.5)		
Macroscopic Type				
elevated	39	9 (23.1)	4.41	0.214
flat	188	22 (11.7)		
Depressed	273	46 (16.9)		
mixed	18	2 (11.1)		
Histological Type				
Differentiated	183	19 (10.4)	5.189	0.023
Undifferentiated	335	60 (17.9)		
Lymphovascular invasion				
Positive	18	6 (33.3)	4.717	0.03
Negative	500	73 (14.6)		

Table 2. Risk Factors for Lymph Node Metastasis by Multivariate Analysis

Factor	OR	95% CI	P-value
Tumor Size >2.0 cm	1.9	1.32-2.84	0.018
Submucosal Invasion	1.6	2.93-5.16	0.029
Undifferentiated	2.4	3.79-14.32	0.012
Lymphovascular invasion	3.1	1.31-6.98	0.014

Table 3. Risk Factors for Lymph Node Metastasis by Multivariate Analysis

Factors	Mucosal gastric cancer		Submucosal gastric cancer	
	95% CI	p value	95% CI	p value
Tumor Size >2.0 cm	0.35-2.44	0.019	10.57-15.67	0.218
Undifferentiated	7.73-24.61	0.14	0.02-4.35	0.014
Lymphovascular invasion	0.01-1.55	0.07	1.72-10.35	0.002

layer, tumor size showed significant correlation with lymph node metastasis. On the other hand, histological type and lymphovascular invasion were independently associated with lymph node metastasis in submucosal gastric carcinoma group (Table 3).

Discussion

Gastric carcinoma is the major cause of cancer related deaths in asia (Baghestani et al., 2009; Lee et al., 2011; Cho et al., 2013). The prognosis is different between early and advanced gastric cancer. The average 5-year survival rate in patients with early gastric cancer is over 90%, and it is up to 94.2% in patients without lymph node metastasis (Noh et al., 2005). The incidence of lymph node metastasis in early gastric cancer range from 2.6% to 4.8% in mucosal cancers and 16.5% to 25% in submucosal cancer (Tsujitani et al., 1999; Kim et al., 2004; Roviello et al., 2006). Treatment options for early gastric cancer include endoscopic resection, wedge resection, laparoscopically assisted gastrectomy and open gastrectomy (Bonenkamp et al., 1999; Soetikno et al., 2005; Kitano et al., 2007). Radical surgery with lymph node dissection has been the standard treatment for early gastric cancer. Because long-term survival after gastrectomy is excellent, considering the lower incidence of lymph node metastasis, endoscopic techniques, such as endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD), have been generally accepted as an alternate treatment to improve the quality of life for selected patients. Endoscopic surgery is technically used to dissect the mucosa or the submucosa layer, with regional lymph nodes left untreated, so the probability of lymph node metastasis is a key criterion for defining subgroup of patients for whom these endoscopic methods are appropriate. Prior to operation, identification of lymph node metastasis can not be achieved via computed tomography or endoscopic ultrasonography because of the lack of reliable criteria for metastatic nodes (Park et al., 2008). Bhandari et al. (2004) reported that the accuracy, sensitivity, and specificity of EUS and three-dimensional multidetector row CT for lymph node staging was, respectively, 79.1%, 57%, and 89.5%, 75%; 57.4%, 89.3% for gastric cancer. Tsendsuren et al. (Tsendsuren et al., 2006) reported that the overall diagnostic accuracy of EUS in preoperative determination of gastric cancer depth of invasion was 68.3% (41/28) and 83.3% (12/10), 60% (20/12), 100% (5/5), 25% (4/1) for T1, T2, T3, and T4, respectively, and the diagnostic accuracy of metastatic lymph node involvement or N staging of EUS was 100% (17/17) for N0 and 41.7% (24/10) for N+, respectively, and 66% (41/27) overall. For this reason, many tumor related variables are currently under investigation as predictors of

lymph node involvement, particularly in Japan and Korea.

In this analysis of a consecutive series of early gastric cancer cases from a single institution, the rate of lymph node metastasis in early gastric cancer was 15.3%, and we found that tumor size >2 cm, submucosal invasion, poor differentiation and lymphovascular invasion were independent risk factors for lymph node metastasis. The positive rates of lymph node metastasis in intramucosal and submucosal lesions were 3.3% and 23.5%, respectively, and the risk factors of lymph node metastasis were quite different from each other. Tumor size showed significant correlation with lymph node metastasis in mucosal carcinoma. On the other side, in submucosal carcinoma, histological type and lymphovascular invasion were independently associated with lymph node metastasis.

According to the literature, tumor size, depth of invasion, histological type, gross appearance, and presence of lymphatic or vascular invasion were related to lymph node metastasis in early gastric cancer (Hyung et al., 2004; Okabayashi et al., 2007; Shen et al., 2009). Gotoda et al. (2000) performed a large study including 5265 patients with early gastric cancer, they reported that undifferentiated early gastric cancer and ulceration were independent factors. Maehara et al. (Maehara et al., 1992) observed that independent risk factors for lymph node metastasis are large tumor dimension, lymphatic involvement and submucosal invasion. Ye et al. (2008) assessed 591 patients with early gastric cancer and found that poorly differentiated early gastric cancers had higher rates of lymph node metastasis. Some research teams reported that being female was associated with lymph node metastasis in both depressed early gastric cancers and differentiated submucosally invasive early gastric cancer (Yasuda et al., 1999; Abe et al., 2004), possibly related to estrogen level (Abe et al., 2002). In the subgroup analysis of early gastric cancer in our studies, female gender was not a significant risk factor for lymph node metastasis. At present, link between gender and lymph node metastasis remains unclear.

When early gastric cancer was subdivided into mucosal and submucosal carcinomas, the risk factors of lymph node metastasis were different from each other. Yamao et al. (Yamao et al., 1996) reported that lymphatic invasion, histological ulceration of tumors and larger tumor sizes are independent risk factors for lymph node metastases in intramucosal early gastric cancer. An et al. (2007) reported that tumor size and lymphatic involvement were independent risk factors for lymph node metastasis in early gastric cancer with submucosal invasion. Shen et al. (2009) reported that histological classification, macroscopic type, tumor size, depth of gastric carcinoma infiltration, and the presence of vascular or lymphatic invasion were significantly and independently related to lymph node metastasis. For intramucosal cancer, tumor size was the unique risk factor for lymph node metastasis. For submucosal cancer, histological classification and tumor size were independent risk factors for lymph node metastasis.

According to the Japanese gastric cancer treatment guideline (Japanese Gastric Cancer Association, 2004), endoscopic surgery is merely indicated in differentiated

mucosal cancers $\leq 2\text{cm}$ in size, whereas submucosal gastric cancers are more suitable for laparoscopic or open gastrectomy with lymphadenectomy. In this study the risk factors of lymph node metastasis of early gastric cancer are in agreement with the Japanese gastric cancer treatment guideline. But these criteria may be too strict and can lead to unnecessary surgery. Some investigators have currently attempted to define the risk factors for lymph node metastasis of submucosal gastric cancer and suggested possible extended criteria for endoscopic treatment. Kurihara et al. (1998) reported that when the submucosal carcinomas were classified into three categories according to depth of invasion by dividing the submucosal (sm) layer into three equal parts, sm1, sm2 and sm3, the incidence of lymph node metastasis increased from 2% to 12% and 29% respectively, sm1 carcinomas with diameters of less than 2cm do not usually metastasize to the lymph nodes. An et al. (2007) reported that no lymph node metastasis was observed in the cases with no lymphatic involvement, SM1 invasion, and tumor size $<1\text{cm}$. The study in a large group of Japanese patients found that in cases where the histology is a differentiated type and without vascular invasion, the rate of lymph node metastasis in submucosal invasion less than $500\mu\text{m}$ was only 0.9% (Ishikawa et al., 2007). Consequently, some highly selected submucosal gastric cancer might be considered as an indication of endoscopic surgery. However, the feasibility of EMR or ESD for this type of early gastric cancer still remains controversial. In our study, lymph node metastasis of submucosal gastric cancer was clinicopathologically related to histological type and lymphovascular invasion. Because this research was a retrospective study without subclassification based on the depth of invasion and in single institution with smaller cases compared with that from Japan, it is reasonable to expect that useful information could be obtained by large-scale prospective studies.

In summary, prediction of lymph node metastasis in early gastric cancer is very important to decide the treatment strategies preoperatively. Endoscopic treatment might be an alternative in differentiated mucosal $\leq 2\text{cm}$ in size gastric cancer patients and some carefully selected submucosal gastric cancer patients.

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