

Clinicopathological Characteristics as Predictive Factors for Lymph Node Metastasis in Submucosal Gastric Cancer

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This work was supported by grants from the National Natural Science Foundation of China (No.30471678) and the Natural Science Foundation of Liaoning (No.200420741).

Received April 17, 2007; accepted July 27, 2007.

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OBJECTIVE To identify clinicopathological characteristics as predictive factors for lymph node metastasis in submucosal gastric cancer, and in addition to establish objective criteria as indications for endoscopic submucosal dissection (ESD).

METHODS Data from 130 patients with submucosal gastric cancer were collected, and the relationship between their clinicopathological characteristics and the presence of lymph node metastasis was retrospectively analyzed by multivariate analysis.

RESULTS In the multivariate logistic regression model, a tumor size of 2 cm or more and an undifferentiated histologic type were found to be independent risk clinicopathological characteristics for lymph node metastasis. Among 130 patients with submucosal carcinoma, no lymph node metastases were observed in 17 patients who showed neither of the two risk clinicopathological characteristics. Lymph node metastasis occurred in 61.1% (22/36) of the patients who had both risk clinicopathological characteristics.

CONCLUSION A tumor size of 2 cm or more and an undifferentiated histologic type were significantly and independently related to lymph node metastasis in submucosal gastric cancer. It is rational for the patients with neither of these two independent risk clinicopathological characteristics to undergo an ESD.

KEYWORDS: early gastric cancer, lymph node, metastasis, clinicopathological characteristics, endoscopic mucosal resection.

INTRODUCTION

Minimally invasive surgeries (MIS) such as endoscopic mucosal resection (EMR) or laparoscopic surgery are performed as a treatment for early gastric cancer. However, MIS should be utilized in conditions where there are no lymph node metastasis. Since the incidence of lymph node metastasis in submucosal gastric cancer has been reported to be only about 20%, it can be expected that the chance of further operations will be reduced if we choose patients with submucosal gastric cancer who have low risk of lymph node metastasis^[1]. At present, the techniques of therapeutic endoscopy for stomach neoplasms are rapidly developing, and endoscopic submucosal dissection (ESD) is a typical example of this development.

Thus, in our study we retrospectively analyzed the clinicopathological characteristics related to lymph node metastasis in submucosal gastric cancers, in order to establish objective criteria to be used as an indication for ESD.

MATERIALS AND METHODS

Patients

A total of 130 patients with submucosal gastric cancer underwent an operation in the Department of Oncology, First Affiliated Hospital of China Medical University, between 1985 and 2006. The criteria used for inclusion in this study were as follows: 1) more than D1 lymph node dissections had been performed^[2]; 2) lymph nodes and the resected specimens had been analyzed for pathological examination. There were 95 male and 35 female patients, with an average age of 55 years (29~80 years). Among the 130 cases, 30 were with and 100 were without node metastasis.

Reference standard

The tumor location, macroscopic type, and histological type were based on the Japanese Classification of Gastric Carcinoma^[3]. The histological types included differentiated and undifferentiated types. Macroscopic types included the following: protruded (type I), superficial elevated (type IIa), flat (type IIb), superficial depressed (type IIc), and excavated (type III). Histological growth patterns included massive, nest, and diffuse types^[4].

Statistical treatment

All data were analyzed using SPSS14.0 statistical software. The clinicopathological parameters between patients with and without lymph node metastasis were determined by the χ^2 test. A multivariate stepwise logistic regression analysis was performed subsequently in order to identify the variables which were considered to have influence on lymph node metastasis. A *P* value of less than 0.05 was considered statistically significant.

RESULTS

Clinicopathological characteristics related to the lymph node metastasis

The relationship on various clinicopathological characteristics and lymph node metastasis was analyzed first by the χ^2 test (Table 1). A tumor size of 2 cm or more, and an undifferentiated histologic type were significantly associated with a higher rate of lymph node metastasis (*P*<0.05). However, no significant relationship was found between lymph node metastasis and sex, age, family medical history, history of past illness, number of tumors, tumor location, macroscopic type or growth pattern.

Table 1. Univariate analysis of potential risk characteristics for lymph node metastasis (cases).

	Lymph node metastasis positive rate (%)	<i>P</i>
Sex		NS
Male	21.05 (20/95)	
Female	28.57 (10/35)	
Age		NS
≤ 60 years	25.64 (20/78)	
> 60 years	23.81 (10/52)	
Family medical history		NS
Positive	47.37 (9/28)	
Negative	19.23 (21/102)	
History of past illness		NS
Positive	22 (11/50)	
Negative	23.75 (19/80)	
Number of tumors		NS
Single	24.39 (30/123)	
Multitude	0 (0/7)	
Tumor location		NS
Upper third	14.29 (1/7)	
Middle third	30.43 (7/23)	
Lower third	22 (22/100)	
Tumor size		0.003
≤ 2 cm	3.45 (1/29)	
> 2 cm	28.71 (29/101)	
Macroscopic type		NS
I	50 (1/2)	
II	25.32 (20/79)	
III	18.37 (9/49)	
Histologic type		0.009
Differentiated	12.90 (8/62)	
Undifferentiated	32.35 (22/68)	
Growth pattern		NS
Massive	23.33 (7/30)	
Nest	12.77 (6/47)	
Diffuse	18.87 (10/53)	

NS, not significant

Multivariate analyses of independent risk characteristics for lymph node metastasis

Among the two characteristics which were observed to have significant correlation with lymph node metastasis by univariate analyses, both characteristics were found to be significantly and independently related to lymph node metastasis by multivariate analysis (*P*<0.05, Table 2).

Table 2. Multivariate analysis of potential risk factors for lymph node metastasis.

Variables*	Odds ratio	95% Confidence interval	P
Tumor size (<2 cm or ≥2 cm)	9.498	1.214~74.335	0.032
Histologic type (differentiated or undifferentiated)	2.922	1.135~7.524	0.026

*Significant factors identified by univariate analysis were included in the multivariate analysis.

Lymph node metastasis in submucosal gastric cancer

Of the 130 patients with submucosal cancer, 30 (23.1%) had lymph node metastasis. The relationship between the two positive risk clinicopathological characteristics and lymph node metastasis was studied. No lymph node metastasis was observed in patients who had neither of the two risk clinicopathological characteristics (0/17). Lymph node metastasis occurred in 61.1% (22/36) of the patients who had both clinicopathological characteristics.

DISCUSSION

The significant achievements of gastric surgeons in the last century in establishing radical surgery with extensive lymph node dissection for gastric cancer, deserve unequivocal respect. However, we now have to proceed to the next stage by improving post-operative function and quality of life after gastric cancer surgery without impairing long-term outcome^[5,6].

MIS, such as EMR or ESD, for gastric cancer is frequently performed in many institutions^[7]. These techniques do preserve gastric function and maintain a high quality of life. However, the treatment strategy for early tumors should therefore be based on a complete cure, and limited surgery must thus have clear indications^[7]. The following indications for EMR for early gastric cancer have generally been accepted: differentiated-type of mucosal cancers without ulcerative findings, with ≤ 2 cm in size if elevated or ≤ 1 cm in size if depressed or flat^[8]. At present, the indications for ESD are still controversial. It has extended through expansion of both theoretical and technical conditions^[9]. In fact, the indication for ESD is strictly confined by two aspects: the possibility of nodal metastases and technical difficulty^[10].

ESD is a highly effective technique enabling surgeons to resect much larger and difficult lesions, which cannot be resected by conventional EMR techniques. ESD is a new endoscopic technique using cutting devices to remove the tumor by the following three steps: 1) injecting fluid into the submucosa to elevate the tumor from the muscle layer; 2) pre-

cutting the surrounding mucosa of the tumor; and 3) dissecting the connective tissue of the submucosa beneath the tumor. So the tumors are resectable in an enbloc fashion, regardless of the size, shape, coexisting ulcer, and location^[9-11]. ESD is gaining acceptance among endoscopists because of its efficacy^[12].

To identify clinicopathological characteristics predictive of lymph node metastasis, definite criteria for predicting lymph node metastasis can lay a foundation for ESD. Still now, some studies thus far have demonstrated that tumor size, gross appearance of the tumor, histological type, and depth of tumor invasion could be predictors of lymph node metastasis in early gastric cancer^[13-15]. In our study, a tumor size of 2 cm or more and an undifferentiated histologic type were significantly associated with a higher rate of lymph node metastasis. No lymph node metastases were observed in patients who had neither of the two risk clinicopathological characteristics, whereas the positive rate of lymph node metastasis was calculated to be 61.1% in patients who had both clinicopathological characteristics.

Regarding the clinical implications on our study, ESD can be performed for the patients without both risk clinicopathological characteristics. As a result, patients without lymph node metastasis do not have to endure possible operative complications and thus are able to avoid risks owing to stomach resection and lymph node dissection. However, the patients with the two risk clinicopathological characteristics have a high potential for lymph node metastasis, and they should receive a lymph node dissection.

In conclusion, knowledge of the risk clinicopathological characteristics provides a simple and useful criterion to indicate ESD for the patients with submucosal gastric cancer. ESD is applicable with promising results, but the technique is still at a developmental stage. Therefore when conducting an endoscopic resection, we must consider the approach to treatment, in terms of the situation and skills of the endoscopist^[16]. Future clinical studies are required to fully develop the indications for, and technique of ESD.

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