

## Retrospective Study

## Feasibility study on expanded indication for endoscopic submucosal dissection of intramucosal poorly differentiated early gastric cancer

Hua Li, Zhi-Bin Huo, Shu-Bo Chen, Hui Li, Dian-Chao Wu, Tong-Shan Zhai, Qi-Hai Xiao, Shu-Xia Wang, Li-Li Zhang

Hua Li, Zhi-Bin Huo, Dian-Chao Wu, Tong-Shan Zhai, Qi-Hai Xiao, Shu-Xia Wang, Li-Li Zhang, Department of Surgical Oncology, Affiliated Xingtai People's Hospital of Hebei Medical University, Xingtai 054001, Hebei Province, China

Shu-Bo Chen, Department of Surgical Urology, Affiliated Xingtai People's Hospital of Hebei Medical University, Xingtai 054001, Hebei Province, China

Hui Li, Department of Hepatobiliary Surgery, Affiliated Xingtai People's Hospital of Hebei Medical University, Xingtai 054001, Hebei Province, China

**Author contributions:** Li H and Huo ZB designed the research; Li H analyzed the data and drafted the manuscript; Chen SB and Li Hui revised the manuscript critically for important intellectual content and contributed to the data analysis; Wu DC, Xiao QH, Wang SX and Zhang LL helped draft the manuscript; all authors read and approved the final manuscript.

**Institutional review board statement:** All procedures performed in studies involving human participants were in accordance with the ethical standards of the Hebei Medical University. Because of the retrospective design, ethics committee approval was not always required.

**Informed consent statement:** All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

**Conflict-of-interest statement:** No conflict of interest was declared by the authors.

**Data sharing statement:** No additional data are available.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on

different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Manuscript source:** Unsolicited manuscript

**Correspondence to:** Dr. Zhi-Bin Huo, Department of Surgical Oncology, Affiliated Xingtai People's Hospital of Hebei Medical University, Xingtai 054001, Hebei Province, China. [huozhibinx@126.com](mailto:huozhibinx@126.com)  
**Telephone:** +86-319-3286154  
**Fax:** +86-319-3286153

**Received:** April 14, 2016

**Peer-review started:** April 15, 2016

**First decision:** May 12, 2016

**Revised:** May 20, 2016

**Accepted:** June 29, 2016

**Article in press:** June 29, 2016

**Published online:** August 7, 2016

### Abstract

**AIM:** To identify clinicopathological factors predictive of lymph node metastasis (LNM) in intramucosal poorly differentiated early gastric cancer (EGC), and further to expand the possibility of using endoscopic submucosal dissection (ESD) for the treatment of intramucosal poorly differentiated EGC.

**METHODS:** Data for 81 surgically treated patients with intramucosal poorly differentiated EGC were collected, and the association between the clinicopathological factors and the presence of LNM was retrospectively analyzed by univariate and multivariate logistic regression analyses. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Several clinicopathologic

factors were investigated to identify predictive factors for lymph nodes metastasis, including gender, age, family history of gastric cancer, number of tumors, tumor location, ulceration, tumor size, macroscopic type, lymphatic vessel involvement, and signet-ring-cell component.

**RESULTS:** Tumor size (OR = 7.273, 95%CI: 1.246-29.918,  $P = 0.042$ ), lymphatic vessel involvement (OR = 42.219, 95%CI: 1.923-97.052,  $P = 0.018$ ) and signet-ring-cell component (OR = 17.513, 95%CI: 1.647-77.469,  $P = 0.034$ ) that were significantly associated with LNM by univariate analysis, were found to be significant and independent risk factors for LNM by multivariate analysis. However, gender, age, family history of gastric cancer, number, location, ulceration and macroscopic type of tumor were found not to be associated with LNM. Of these 81 patients diagnosed with intramucosal poorly differentiated EGC, 7 (8.6%) had LNM. The LNM rates were 9.1%, 22.2% and 57.1%, respectively, in cases with one, two and three of the risk factors. There was no LNM in 54 patients without the three risk clinicopathological factors.

**CONCLUSION:** Tumor size, lymphatic vessel involvement and signet-ring-cell component are independently associated with the presence of LNM in intramucosal poorly differentiated EGC. Thus, these three risk factors may be used as a simple criterion to expand the possibility of using ESD for the treatment of intramucosal poorly differentiated EGC.

**Key words:** Intramucosal poorly differentiated early gastric cancer; Early gastric cancer; Clinicopathological characteristics; Lymph node metastasis; Endoscopic submucosal dissection

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** Endoscopic submucosal dissection (ESD) has recently been practiced on a differentiated type of early gastric cancer (EGC). However, there is no clear evidence for endoscopic treatment of intramucosal poorly differentiated EGC. We carried out this retrospectively study to determine the clinicopathological factors that are predictive of lymph node metastasis in intramucosal poorly differentiated EGC, and to guide the individual application of ESD in a suitable subgroup of patients with intramucosal poorly differentiated EGC.

Li H, Huo ZB, Chen SB, Li H, Wu DC, Zhai TS, Xiao QH, Wang SX, Zhang LL. Feasibility study on expanded indication for endoscopic submucosal dissection of intramucosal poorly differentiated early gastric cancer. *World J Gastroenterol* 2016; 22(29): 6736-6741 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v22/i29/6736.htm> DOI: <http://dx.doi.org/10.3748/wjg.v22.i29.6736>

## INTRODUCTION

The minimalization of therapeutic invasiveness to preserve quality of life is a major topic in the management of early gastric cancer (EGC). Endoscopic submucosal dissection (ESD) has been widely accepted as an alternative treatment to surgery for EGC<sup>[1-3]</sup>. This minimally invasive technique could be used in EGC management as well as avoiding risk of lymph node metastasis (LNM)<sup>[4-9]</sup>. For the reason of higher LNM risk in undifferentiated EGC, ESD application has been limited to well or moderately differentiated EGC with a diameter smaller than 2 cm and confined to the mucosa without ulceration<sup>[10,11]</sup>. Thus, gastrectomy with lymphadenectomy is now considered an indispensable treatment for patients with undifferentiated EGC. Undifferentiated gastric cancer was divided into signet ring cell carcinoma, poorly differentiated adenocarcinoma, and mucinous adenocarcinoma<sup>[12]</sup>. Nevertheless, about 96.6% of poorly differentiated EGC cases which are limited to the mucosa, were found not to have LNM<sup>[13]</sup>, indicating that gastrectomy with lymphadenectomy may be an overtreatment among them.

Thus, we performed this current retrospective study to identify the clinicopathological factors which can be predictive in diagnosis of LNM in poorly differentiated EGC, and to guide the individual application of ESD in a suitable subgroup of patients with intramucosal poorly differentiated EGC.

## MATERIALS AND METHODS

### Patients

The patients were enrolled from the Department of Oncology, Affiliated Xingtai People's Hospital of Hebei Medical University, Xingtai, China between January 1987 and December 2007, and all these patients had undergone a radical check for identification of EGC.

The patients who met the following inclusion criteria were enrolled: (1) Patients who underwent lymph node dissection beyond limited (D1) dissection; (2) Patients who were diagnosed with intramucosal poorly differentiated EGC by pathological analysis of lymph nodes and resected specimens according to the Japanese Classification of Gastric Carcinoma (JCGC)<sup>[12]</sup>; and (3) Records can be retrieved in database.

Eighty-one patients (23 females and 58 males; mean age: 48 years; age range: 29 to 79 years) were identified to meet the inclusion criteria and were included for the following analysis.

The study protocol was approved by the Ethics Committee of Hebei Medical University.

### Classification and dissection of lymph nodes

All the lymph nodes from each case were dissected with great care from the *en bloc* specimens, and a well-

**Table 1** Univariate analysis of potential risk characteristics for lymph node metastasis *n* (%)

Factor	Number of cases with lymph node metastasis	<i>P</i> value
Sex		
Male ( <i>n</i> = 58)	4 (6.9)	0.421
Female ( <i>n</i> = 23)	3 (13.0)	
Age (yr)		
< 60 ( <i>n</i> = 39)	2 (5.1)	0.319
≥ 60 ( <i>n</i> = 42)	5 (11.9)	
Family history		
Positive ( <i>n</i> = 15)	3 (20.0)	0.126
Negative ( <i>n</i> = 66)	4 (6.1)	
Number of tumors		
Single ( <i>n</i> = 77)	6 (7.8)	0.305
Multitude ( <i>n</i> = 4)	1 (25.0)	
Location		
Upper ( <i>n</i> = 6)	1 (16.7)	0.247
Middle ( <i>n</i> = 16)	3 (18.8)	
Lower ( <i>n</i> = 59)	3 (5.1)	
Ulceration		
Negative ( <i>n</i> = 70)	5 (71.4)	0.284
Positive ( <i>n</i> = 11)	2 (18.2)	
Tumor size in diameter		
< 2 cm ( <i>n</i> = 59)	2 (3.4)	0.015
≥ 2 cm ( <i>n</i> = 22)	5 (22.7)	
Macroscopic type		
I ( <i>n</i> = 4)	1 (25.0)	0.524
II ( <i>n</i> = 43)	4 (9.3)	
III ( <i>n</i> = 34)	2 (5.9)	
Lymphatic vessel involvement		
Negative ( <i>n</i> = 67)	1 (1.5)	< 0.001
Positive ( <i>n</i> = 14)	6 (42.9)	
Signet-ring-cell component <sup>1</sup>		
Absence ( <i>n</i> = 74)	4 (5.4)	0.006
Presence ( <i>n</i> = 7)	3 (42.9)	

<sup>1</sup>Intermingled components of signet-ring-cell cancer cells within a cancerous lesion.

trained surgeon was appointed to classify the dissected lymph nodes after she or he reviewed the excised specimens carefully based on the JCGC<sup>[12]</sup>. Afterward, the lymph nodes were sectioned and then stained with eosin and hematoxylin, followed by pathological examination for lymphatic vessel involvement (LVI) and metastasis using immunohistochemistry with D2-40.

### Association between clinicopathological parameters and LNM

Clinicopathological parameters from the JCGC<sup>[12]</sup> were included in this current study, which consisted of gender (female and male), age (< 60 years and ≥ 60 years), family history of gastric cancer, tumor number (single or multitude), tumor location (in lower, middle, or upper location of the stomach), ulceration, tumor size (maximum diameter ≥ 2 cm or < 2 cm), macroscopic type [protruded (type I), superficially elevated (type II a), flat (type II b), superficially depressed (type II c), or excavated (type III)], lymphatic vessel involvement, signet-ring-cell component (intermingled components

of signet-ring-cell cancer cells within a cancerous lesion). The association between LNM and various clinicopathological factors was examined as described below.

### Statistical analysis

All data were analyzed using SPSS18.0 (Chicago, IL, United States). The differences between patients with and without LNM in the clinicopathological parameters were determined by the  $\chi^2$  test. Independent risk factors for LNM were determined using multivariate stepwise logistic regression analysis. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. *P* < 0.05 was considered statistically significant.

## RESULTS

### Association between clinicopathological parameters and LNM

The association between LNM and various clinicopathological characteristics was determined by  $\chi^2$  test (Table 1). Tumor diameter ≥ 2.0 cm, LVI, and signet-ring-cell cancer cell intermingled components were significantly associated with a high LNM rate (*P* < 0.05 for all).

On the other side, gender, age, family history of gastric cancer, tumor number, ulceration, location and type showed no significant association with LNM.

### Multivariate analysis of potential independent risk factors for LNM

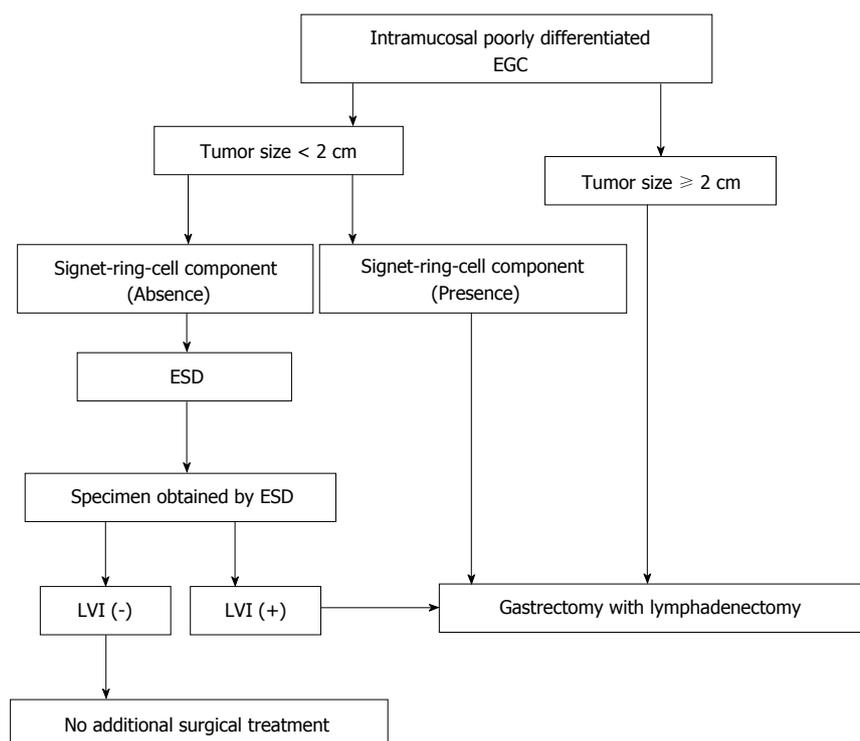
Multivariate analysis results showed that the factors which were significantly associated with a high LNM rate from univariate analysis were also significant for LNM (*P* < 0.05 for both) and are independent risk factors for LNM (Table 2).

### LNM in intramucosal poorly differentiated EGC

Of the 81 cases, LNM was diagnosed by histology in 7 (8.6%) patients. The LNM rates were 9.1%, 22.2% and 57.1% in intramucosal poorly-differentiated EGC for patients with one, two or three risk factors, respectively. LNM was not found in other 54 patients without one or more of three risk factors (Table 3).

## DISCUSSION

As a result of advances in diagnostic technology, including both the radiologic and endoscopic modalities, the detection rate of EGC has increased. Since EGC is associated with a favorable prognosis, many efforts and studies have been made to minimize resection invasiveness. Endoscopic mucosal resection (EMR) and ESD are included in the treatment of EGC. Compared with EMR, ESD has an advantage of allowing *en bloc* resection by dissection at submucosal location, which leads to accurate pathologic assessment of specimens<sup>[14-16]</sup>. ESD can maintain gastric function and



**Figure 1** Flow chart of the therapeutic strategy for cases with intramucosal poorly differentiated early gastric cancer. LVI: Lymphatic vessel involvement; EGC: Early gastric cancer; ESD: Endoscopic submucosal dissection.

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

Characteristic	OR	95%CI	P value
Tumor size	7.273	1.246-29.918	0.042
< 2 cm			
≥ 2 cm			
Lymphatic vessel involvement	42.219	1.923-97.052	0.018
Negative			
Positive			
Signet-ring-cell component	17.513	1.647-77.469	0.034
Absence			
Presence			

keep a high life quality<sup>[17-22]</sup>. Nevertheless, currently the application of ESD is confined to differentiated EGC. One reason for choosing ESD is whether the presence of LNM or not can be precisely predicted. Thus, we tried to broaden the application of ESD to poorly differentiated EGC using retrospective examination of intramucosal poorly differentiated EGC to confirm how LNM can be predicted.

The multivariate and univariate analysis results indicated that a tumor  $\geq 2.0$  cm, LVI, and intermingled components of signet-ring-cell cancer cells were factors to predict LNM for patients with intramucosal poorly differentiated EGC. Current study results together with results from previous reports about undifferentiated EGC demonstrate that there is a significant correlation of the presence of LVI, large tumor and submucosal

invasion with high LNM rate<sup>[23-30]</sup>.

We tried to determine a subgroup of patients with intramucosal poorly differentiated EGC among whom we can rule out the risk of LNM, *i.e.*, candidates who can be cured by ESD. Interestingly, we have not found LNM in patients without one or more of the three risk factors. This may be due to that ESD is sufficient in treating these cases, and no additional surgery is needed.

We further studied the association between the LNM rate and the number of three risk factors (tumor  $\geq 2.0$  cm, presence of LVI, and intermingled components of signet-ring-cell cancer cells) so that we can have a simple criterion to confirm what is an ideal treatment strategy for intramucosal poorly differentiated EGC. In the current study, the LNM rates were 9.1%, 22.2%, and 57.1% in cases with one, two or three risk factors, respectively. Therefore, for these patients gastrectomy with lymphadenectomy may be a better choice.

The present study has some limitations. First, this is a single-center retrospective study. Second, the small sample size was small. Thus, the results may not be sufficient to come to a definitive conclusion.

As the study results suggest, we would like to propose a new treatment for patients with intramucosal poorly differentiated EGC (Figure 1). For patients without any of the risk factors, ESD without lymphadenectomy is sufficient. When LVI is confirmed in specimens, gastrectomy with lymphadenectomy may be a better choice for these patients.

**Table 3 Relationship between the number of risk factors (a tumor larger than or equal to 2.0 cm, the presence of lymphatic vessel involvement, and the presence of intermingled components of signet-ring-cell cancer cells) and lymph node metastasis in intramucosal poorly differentiated early gastric cancer**

Number of risk factors	Lymph metastasis rate
None	0% (0/54)
One	9.1% (1/11)
Two	22.2% (2/9)
Three	57.1% (4/7)

## COMMENTS

### Background

Gastrectomy with lymphadenectomy is a standard treatment for patients with poorly differentiated early gastric cancer (EGC) with lymph node metastasis (LNM). Nevertheless, about 96.6% of cases are confined to mucosa, otherwise many (approximately 80%) patients with submucosal extension were demonstrated not to have LNM, and for these patients, gastrectomy with lymphadenectomy might be an overtreatment. The authors tried to determine a subgroup of patients with intramucosal poorly differentiated EGC among whom we can rule out the risk of LNM so that these patients can be treated by endoscopic submucosal dissection (ESD), and this may be a breakthrough treatment for poorly differentiated EGC.

### Research frontiers

Some previous studies have tried to determine the risk factors which can predict LNM in EGC. However, only few reports have studied the possible applicability of ESD.

### Innovations and breakthroughs

In poorly differentiated EGC, lymphatic vessel involvement, depth of invasion and tumor size were demonstrated to be independent risk factors for LNM. Additionally, the study developed a simple criterion which can help increase the usage of ESD to treat intramucosal poorly differentiated EGC.

### Applications

The results of predictive factors of LNM suggest that ESD is an optional choice for treatment of intramucosal poorly differentiated EGC.

### Terminology

Compared with EMR, ESD has an advantage of allowing *en bloc* resection by dissection at submucosal location, which leads to accurate pathologic assessment of specimens. ESD can maintain gastric function and keep a high life quality and is an optional technique for minimally invasive treatment.

### Peer-review

In the present study, authors identified predictive factors for LNM in intramucosal poorly differentiated EGC, and expanded usage of ESD for intramucosal poorly differentiated EGC treatment. Results indicated that tumor size, lymphatic vessel involvement and signet-ring-cell component that were significantly associated with LNM by univariate analysis, were found to be significant and independent risk factors for LNM by multivariate analysis.

## REFERENCES

- Kang KJ, Kim KM, Min BH, Lee JH, Kim JJ. Endoscopic submucosal dissection of early gastric cancer. *Gut Liver* 2011; **5**: 418-426 [PMID: 22195238 DOI: 10.5009/gnl.2011.5.4.418]
- Mukasa M, Takedatsu H, Matsuo K, Sumie H, Yoshida H, Hinosaka A, Watanabe Y, Tsuruta O, Torimura T. Clinical characteristics and management of gastric tube cancer with endoscopic submucosal dissection. *World J Gastroenterol* 2015; **21**: 919-925 [PMID: 25624726 DOI: 10.3748/wjg.v21.i3.919]
- Hoteya S, Yahagi N, Iizuka T, Kikuchi D, Mitani T, Matsui A, Ogawa O, Yamashita S, Furuhashi T, Yamada A, Kimura R, Nomura K, Kuribayashi Y, Kaise M. Endoscopic submucosal dissection for nonampullary large superficial adenocarcinoma/adenoma of the duodenum: feasibility and long-term outcomes. *Endosc Int Open* 2013; **1**: 2-7 [PMID: 26135505 DOI: 10.1055/s-0033-1359232]
- Koeda K, Nishizuka S, Wakabayashi G. Minimally invasive surgery for gastric cancer: the future standard of care. *World J Surg* 2011; **35**: 1469-1477 [PMID: 21476116 DOI: 10.1007/s00268-011-1051-5]
- Nozaki I, Kubo Y, Kurita A, Tanada M, Yokoyama N, Takiyama W, Takashima S. Long-term outcome after laparoscopic wedge resection for early gastric cancer. *Surg Endosc* 2008; **22**: 2665-2669 [PMID: 18363067 DOI: 10.1007/s00464-008-9795-1]
- Yoshida K, Yamaguchi K, Okumura N, Osada S, Takahashi T, Tanaka Y, Tanabe K, Suzuki T. The roles of surgical oncologists in the new era: minimally invasive surgery for early gastric cancer and adjuvant surgery for metastatic gastric cancer. *Pathobiology* 2011; **78**: 343-352 [PMID: 22104206 DOI: 10.1159/000328197]
- Fatourou E, Roukos DH. Endoscopic submucosal dissection: can it safely expand indications for a minimally invasive approach to patients with early gastric cancer? *Surg Endosc* 2010; **24**: 1793-174; author reply 1795 [PMID: 20041265 DOI: 10.1007/s00464-009-0844-1]
- Hyung WJ, Cheong JH, Kim J, Chen J, Choi SH, Noh SH. Application of minimally invasive treatment for early gastric cancer. *J Surg Oncol* 2004; **85**: 181-185; discussion 186 [PMID: 14991872]
- Son T, Kwon IG, Hyung WJ. Minimally invasive surgery for gastric cancer treatment: current status and future perspectives. *Gut Liver* 2014; **8**: 229-236 [PMID: 24827617 DOI: 10.5009/gnl.2014.8.3.229]
- Ono H, Kondo H, Gotoda T, Shirao K, Yamaguchi H, Saito D, Hosokawa K, Shimoda T, Yoshida S. Endoscopic mucosal resection for treatment of early gastric cancer. *Gut* 2001; **48**: 225-229 [PMID: 11156645 DOI: 10.1136/gut.48.2.225]
- Abe N, Watanabe T, Suzuki K, Machida H, Toda H, Nakaya Y, Masaki T, Mori T, Sugiyama M, Atomi Y. Risk factors predictive of lymph node metastasis in depressed early gastric cancer. *Am J Surg* 2002; **183**: 168-172 [PMID: 11918883 DOI: 10.1016/S0002-9610(01)00860-1]
- Japanese Gastric Cancer Association. Japanese Classification of Gastric Carcinoma - 2nd English Edition - *Gastric Cancer* 1998; **1**: 10-24 [PMID: 11957040 DOI: 10.1007/PL00011681]
- Park YD, Chung YJ, Chung HY, Yu W, Bae HI, Jeon SW, Cho CM, Tak WY, Kweon YO. Factors related to lymph node metastasis and the feasibility of endoscopic mucosal resection for treating poorly differentiated adenocarcinoma of the stomach. *Endoscopy* 2008; **40**: 7-10 [PMID: 18210339 DOI: 10.1055/s-2007-966750]
- Kakushima N, Fujishiro M, Kodashima S, Muraki Y, Tateishi A, Yahagi N, Omata M. Technical feasibility of endoscopic submucosal dissection for gastric neoplasms in the elderly Japanese population. *J Gastroenterol Hepatol* 2007; **22**: 311-314 [PMID: 17295759 DOI: 10.1111/j.1440-1746.2006.04563.x]
- Yamamoto H, Kawata H, Sunada K, Sasaki A, Nakazawa K, Miyata T, Sekine Y, Yano T, Satoh K, Ido K, Sugano K. Successful *en bloc* resection of large superficial tumors in the stomach and colon using sodium hyaluronate and small-caliber-tip transparent hood. *Endoscopy* 2003; **35**: 690-694 [PMID: 12929067 DOI: 10.1055/s-2003-41516]
- Yokoi C, Gotoda T, Hamanaka H, Oda I. Endoscopic submucosal dissection allows curative resection of locally recurrent early gastric cancer after prior endoscopic mucosal resection. *Gastrointest Endosc* 2006; **64**: 212-218 [PMID: 16860071 DOI: 10.1016/j.gie.2005.10.038]
- Lee JH, Kim JG, Jung HK, Kim JH, Jeong WK, Jeon TJ, Kim JM, Kim YI, Ryu KW, Kong SH, Kim HI, Jung HY, Kim YS, Zang DY, Cho JY, Park JO, Lim do H, Jung ES, Ahn HS, Kim HJ. Clinical practice guidelines for gastric cancer in Korea: an evidence-based approach. *J Gastric Cancer* 2014; **14**: 87-104 [PMID: 25061536 DOI: 10.5230/jgc.2014.14.2.87]

- 18 **Kitagawa Y**, Kitano S, Kubota T, Kumai K, Otani Y, Saikawa Y, Yoshida M, Kitajima M. Minimally invasive surgery for gastric cancer--toward a confluence of two major streams: a review. *Gastric Cancer* 2005; **8**: 103-110 [PMID: 15864717 DOI: 10.1007/s10120-005-0326-7]
- 19 **Makuuchi H**, Kise Y, Shimada H, Chino O, Tanaka H. Endoscopic mucosal resection for early gastric cancer. *Semin Surg Oncol* 1999; **17**: 108-116 [PMID: 10449682 DOI: 10.1002/(SICI)1098-2388(199909)17:2<108::AID-SSU5>3.0.CO;2-8]
- 20 **Ishikawa S**, Togashi A, Inoue M, Honda S, Nozawa F, Toyama E, Miyanari N, Tabira Y, Baba H. Indications for EMR/ESD in cases of early gastric cancer: relationship between histological type, depth of wall invasion, and lymph node metastasis. *Gastric Cancer* 2007; **10**: 35-38 [PMID: 17334716 DOI: 10.1007/s10120-006-0407-2]
- 21 **Oda I**, Saito D, Tada M, Iishi H, Tanabe S, Oyama T, Doi T, Otani Y, Fujisaki J, Ajioka Y, Hamada T, Inoue H, Gotoda T, Yoshida S. A multicenter retrospective study of endoscopic resection for early gastric cancer. *Gastric Cancer* 2006; **9**: 262-270 [PMID: 17235627 DOI: 10.1007/s10120-006-0389-0]
- 22 **Oka S**, Tanaka S, Kaneko I, Mouri R, Hirata M, Kawamura T, Yoshihara M, Chayama K. Advantage of endoscopic submucosal dissection compared with EMR for early gastric cancer. *Gastrointest Endosc* 2006; **64**: 877-883 [PMID: 17140890 DOI: 10.1016/j.gie.2006.03.932]
- 23 **Kim YY**, Jeon SW, Kim J, Park JC, Cho KB, Park KS, Kim E, Chung YJ, Kwon JG, Jung JT, Kim EY, Kim KO, Jang B, Lee SH, Yang CH. Endoscopic submucosal dissection for early gastric cancer with undifferentiated histology: could we extend the criteria beyond? *Surg Endosc* 2013; **27**: 4656-4662 [PMID: 23943115 DOI: 10.1007/s00464-013-3099-9]
- 24 **Kim KJ**, Park SJ, Moon W, Park MI. Analysis of factors related to lymph node metastasis in undifferentiated early gastric cancer. *Turk J Gastroenterol* 2011; **22**: 139-144 [PMID: 21796549 DOI: 10.4318/tjg.2011.0182]
- 25 **Li C**, Kim S, Lai JF, Oh SJ, Hyung WJ, Choi WH, Choi SH, Zhu ZG, Noh SH. Risk factors for lymph node metastasis in undifferentiated early gastric cancer. *Ann Surg Oncol* 2008; **15**: 764-769 [PMID: 18043971 DOI: 10.1245/s10434-007-9707-y]
- 26 **Lee H**, Lee JH. Expanding indications of endoscopic submucosal dissection for early gastric cancer: hope or hype? *Gut Liver* 2015; **9**: 135-136 [PMID: 25720997 DOI: 10.5009/gnl15008]
- 27 **Ichikura T**, Uefuji K, Tomimatsu S, Okusa Y, Yahara T, Tamakuma S. Surgical strategy for patients with gastric carcinoma with submucosal invasion. A multivariate analysis. *Cancer* 1995; **76**: 935-940 [PMID: 8625218]
- 28 **Lee H**, Yun WK, Min BH, Lee JH, Rhee PL, Kim KM, Rhee JC, Kim JJ. A feasibility study on the expanded indication for endoscopic submucosal dissection of early gastric cancer. *Surg Endosc* 2011; **25**: 1985-1993 [PMID: 21136092 DOI: 10.1007/s00464-010-1499-7]
- 29 **Kunisaki C**, Takahashi M, Nagahori Y, Fukushima T, Makino H, Takagawa R, Kosaka T, Ono HA, Akiyama H, Moriwaki Y, Nakano A. Risk factors for lymph node metastasis in histologically poorly differentiated type early gastric cancer. *Endoscopy* 2009; **41**: 498-503 [PMID: 19533552 DOI: 10.1055/s-0029-1214758]
- 30 **Komatsu S**, Ichikawa D, Miyamae M, Shimizu H, Konishi H, Shiozaki A, Fujiwara H, Okamoto K, Kishimoto M, Otsuji E. Histological mixed-type as an independent prognostic factor in stage I gastric carcinoma. *World J Gastroenterol* 2015; **21**: 549-555 [PMID: 25593472 DOI: 10.3748/wjg.v21.i2.549]

**P- Reviewer:** Chandrakesan P, McHenry L **S- Editor:** Gong ZM  
**L- Editor:** Wang TQ **E- Editor:** Wang CH





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: [bpgooffice@wjgnet.com](mailto:bpgooffice@wjgnet.com)

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>



ISSN 1007-9327



9 771007 932045