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

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Hua Li and Huo ZB designed the research; Li H analyzed the data and drafted the manuscript; Chen SB and Li H 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.

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

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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.

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[1-3]. This minimally invasive technique could be used in EGC management as well as avoiding risk of lymph node metastasis (LNM)[4-9]. 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[10,11]. 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[12]. Nevertheless, about 96.6% of poorly differentiated EGC cases which are limited to the mucosa, were found not to have LNM[13], 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)[12]; 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-
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| Table 1 Univariate analysis of potential risk characteristics for lymph node metastasis n (%) |
|----------------------------------|-----------------|--------------------------|
| Factor                          | Number of cases | P value                 |
| Sex                             | Male (n = 58)   | 4 (6.9)                  | 0.421                     |
|                                 | Female (n = 23) | 3 (13.0)                 |                           |
| Age (yr)                        | < 60 (n = 39)   | 2 (5.1)                  | 0.319                     |
|                                 | ≥ 60 (n = 42)   | 5 (11.9)                 |                           |
| Family history                  | Positive (n = 15)| 3 (20.0)                | 0.126                     |
|                                 | Negative (n = 66)| 4 (6.1)                 |                           |
| Number of tumors                | Single (n = 77) | 6 (7.8)                  | 0.305                     |
|                                 | Multitude (n = 4)| 1 (25.0)                |                           |
| Location                        | Upper (n = 6)   | 1 (16.7)                 | 0.247                     |
|                                 | Middle (n = 16) | 3 (18.8)                 |                           |
|                                 | Lower (n = 59)  | 3 (5.1)                  |                           |
| Ulceration                      | Negative (n = 70) | 5 (71.4)                | 0.284                     |
|                                 | Positive (n = 11)| 2 (18.2)                |                           |
| Tumor size in diameter          | < 2 cm (n = 59) | 2 (3.4)                  | 0.015                     |
|                                 | ≥ 2 cm (n = 22) | 5 (22.7)                 |                           |
| Macropscopic type               | I (n = 4)       | 1 (25.0)                 | 0.524                     |
|                                 | II (n = 43)     | 4 (9.3)                  |                           |
|                                 | III (n = 34)    | 2 (5.9)                  |                           |
| Lymphatic vessel involvement    | Negative (n = 67)| 1 (1.5)                  | < 0.001                   |
|                                 | Positive (n = 14)| 6 (42.9)                |                           |
| Signet-ring-cell component      | Absence (n = 74) | 4 (5.4)                  | 0.006                     |
|                                 | Presence (n = 7) | 3 (42.9)                 |                           |

\(^{1}\)Intermingled components of signet-ring-cell cancer cells within a cancerous lesion.

Association between clinicopathological parameters and LNM

Clinicopathological parameters from the JCGC\(^{12}\) 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 III 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\(^{14-16}\). ESD can maintain gastric function and
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 size ≥ 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 2 Multivariate analysis of potential risk factors for lymph node metastasis**

| Characteristic                      | OR    | 95%CI        | P value |
|-------------------------------------|-------|--------------|---------|
| Tumor size < 2 cm                   | 1.246-29.918 | 0.042       |
| Tumor size ≥ 2 cm                   | 42.219 | 1.923-97.052 | 0.018   |
| Lymphatic vessel involvement        | 17.513 | 1.647-77.469 | 0.034   |

**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 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, and 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 minimal 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.

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