**Name of journal:** ***World Journal of Gastroenterology***

**ESPS Manuscript NO: 26547**

**Manuscript type: ORIGINAL ARTICLE**

***Retrospective Study***

**feasibility study on the expanded indication for endoscopic submucosal dissection of intramucosal poorly differentiated early gastric cancer**

Li H *et al*. Expanded indication for endoscopic submucosal dissection

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**Author contributions**: Huo ZB, Li H designed the research; Li H analyzed the data and drafted the manuscript; Chen SB and Li HU revised the manuscript critically for important intellectual content and contributed to the data analysis; Wu DC, Xiao QH, Wang SX, and Zhang LL helped drafting 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, approval of the ethic commission 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.

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**Manuscript source:** Unsolicited manuscript

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**Received:** April 14, 2016

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

**First decision:** May 12, 2016

**Revised:** May 20, 2016

**Accepted:** June 28, 2016

**Article in press:**

**Published online:**

**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 from 81 patients with intramucosal poorly differentiated EGC and surgically treated 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 (OR) with 95% confidence interval (95%CI) were calculated. Several clinicopathologic factors were being investigated in order to identify predictive factors for lymph nodes metastasis: gender, age, family medical history of gastric cancer, number of tumors, the location of the tumor, ulceration, tumor size, macroscopic type, lymphatic vessel involvement, signet-ring-cell component.

**RESULTS:** The 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 medical history of gastric cancer, number, location, ulceration and macroscopic type of the 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 respectively in intramucosal poorly differentiated EGC. There was no LNM in 54 patients without the three risk clinicopathological factors.

**CONCLUSION:** The 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 to set 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; Lymph node metastasis; Clinicopathological characteristics; 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 treatments 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 HU, Wu DC, Xiao QH, Wang SX, Zhang LL.feasibility study on the expanded indication for endoscopic submucosal dissection of intramucosal poorly differentiated early gastric cancer*. World J Gastroenterol* 2016; In press

**INTRODUCTION**

The minimalization of therapeutic invasiveness in order 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 metastases (LNM)[4-9]. For the reason of higher lymph node metastasis (LNM) risk in undifferentiated EGC, ESD application has been limited in EGC of well or moderately differentiated histology with diameter smaller than 2 cm and confined to the mucosa without ulceration[10,11]. Thus, gastrectomy with lymphadenectomy is now considered as an indispensable treatment for patients who are with undifferentiated EGC. Undifferentiated gastric cancer was divided into signet ring cell carcinoma, poorly differentiated adenocarcinoma, and mucinous adenocarcinoma[12]. Nevertheless, about 96.6% poorly differentiated EGC cases which are limited to the mucosa, were found to be without LNM[13], indicating 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 diagnose 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.

**METERIALS AND METHODS**

***Patients***

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

The patients who met the following inclusion criteria were enrolled: (1) Patients who perfromed lymph node dissection beyond limited (D1) dissection ; (2) Diagnosed as intramucosal poorly differentiated EGC by pathologically analyzation 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 female,58 male with a mean age of 48 years and age ranges from 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 dessection and of lymph nodes***

All the lymph nodes from each case were dissected with great care from the enbloc specimens, and a well trained surgeon was appointed to classify the dissected lymph nodes after she or he reviewed the excised specimens carefully based on the JCGC[12]. Afterward, the lymph nodes were sectioned and then stained with eosin and hematoxylin, following pathological examination for lymphatic vessel involvement (LVI) and metastasis using immunohistochemistry with D2-40.

***Association between clinicopathological parameters and lymph node metastasis***

Clinicopathological parameters from the JCGC[12] were included in this current study which consist of gender (female and male), age (< 60 years, and ≥ 60 years), family gastric cancer history, tumor number (single or multitude), tumor location (in lower, middle, or upper location of stomach), ulceration, tumor size (maximum diameter ≥ 2 cm, or < 2 cm), macroscopic type [protruded (type I), superficial elevated (type IIa), flat (type IIb), superficial depressed (type IIc), 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 following.

***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 *χ2* test. Independent risk factors for LNM was determined using multivariate stepwise logistic regression analysis. CI of 95% and hazard ratio were calculated. *P*＜0.05 was considered to be statistically significant.

**RESULTS**

***Association between clinicopathological parameters and lymph node metastasis***

The association between LNM and various clinicopathological characteristics was determined by *χ2* test (shown in table 1). Tumor ≥ 2.0 cm, LVI, and signet-ring-cell cancer cell intermingled components were all significantly associated with higher LNM rate (all *P* < 0.05).

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

***Multivariate analysis of potential independent risk clinicopathological factors for lymph node metastasis***

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

***Lymph node metastasis 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 who are with one, two or three risk factors, respectively. LNM was not found in other 54 patients who are 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 incidence of EGC has increased. Since EGC’s association with favorable prognosis, many efforts and researches had 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 keep it of a high life quality[17-22]. Nevertheless, currently the application of ESD is confined to differentiated EGC. One reason for choosing ESD is whether the patient is with LNM or not can be precisely predicted. Thus, we tried to broaden the application of ESD to EGC of poorly differentiation 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 ≥2.0 cm, LVI, and intermingled components of signet-ring-cell cancer cells were factors to predict LNM for patients who are with intramucosal poorly differentiated EGC. Current study results together with results from previous reports about undifferentiated EGC can demonstrate there is a significant correlation between presence of LVI, large tumor and submucosal invasion with high LNM rate[23-29].

After that we tried to determine a subgroup from patients of 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.

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

Still, in present study some limitations exist. First, this is a retrospective analysis with only one center. Secondly, there is just a relatively small sample size. Thus, the results may not be sufficient to com to a definitive conclusion.

As the study results suggests, we would like to propose a new treatment for patients who are with intramucosal poorly differentiated EGC (shown in Figure 1). For patients without any of the risk factors, ESD without lymphadenectomy is sufficient. The particularly LVI becomes first evidence by histological examination of the entire ESD obtained specimen. When LVI was tested out in specimens, gastrectomy with lymphadenectomy may be a better choice for these patients.

**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% cases confined to mucosa, otherwise many (approximately 80%) patients who are with submucosal extension were demonstrated to be without LNM, and for these patients, gastrectomy with lymphadenectomy might be overtreatment We tried to determine a subgroup from patients of intramucosal poorly differentiated EGC among whom we can rule out the risk of LNM ,so patients can be treated with 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 of LNM. Additionally, the study build up 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 it of a high life quality and is an optional technique for minimally invasive treatment.

***Peer review***

In 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 the 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**

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**P-Reviewer:** Chandrakesan P, McHenry L **S-Editor:** Gong ZM

**L-Editor:** **E-Editor:**

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

|  |  |  |
| --- | --- | --- |
| **Factor** | **Positive number of**  **lymph node metastasis** | ***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 medical 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) |  |
| Macroscopic 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 component1 |  |  |
| Absence (*n* = 74) | 4 (5.4) | 0.006 |
| Presence (*n* = 7) | 3 (42.9) |  |

1intermingled components of signet-ring-cell cancer cells within a cancerous lesion.

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

|  |  |  |  |
| --- | --- | --- | --- |
| **Characteris** | **Hazard ratio** | **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 |  |  |  |

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

**LVI (+)**

**LVI (-)**

**Intramucosal poorly differentiated EGC**

**No additional surgical treatment**

**Gastrectomy with lymphadenectomy**

**Specimen obtained by ESD**

**Tumor size ≥ 2 cm**

**Tumor size < 2 cm**

**Signet-ring-cell component**

**(Absence)**

**Signet-ring-cell component**

**(Presence)**

**ESD**

**Figrue 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.