The risk of lymph node metastases in 3951 surgically resected mucosal gastric cancers: implications for endoscopic resection CME

Kang Kook Choi, MD, PhD,[1] Jae Moon Bae, MD, PhD,[2] Su Mi Kim, MD,[2] Tae Sung Sohn, MD, PhD,[2] Jae Hyung Noh, MD, PhD,[2] Jun Ho Lee, MD, PhD,[2] Min-Gew Choi, MD, PhD,[2] Sung Kim, MD, PhD[2]

Seoul, Republic of Korea

Background and Aims: Endoscopic resection for mucosal gastric cancer (MGC) is highly recommended in the absence of lymph node metastasis (LNM). We aimed to clarify the risk factors for LNM in MGC and to investigate the association of LNM with the indication criteria for endoscopic submucosal dissection (ESD).

Methods: A retrospective cohort study was performed on 3951 patients with MGC who underwent radical gastrectomy at the Samsung Medical Center in Seoul, Republic of Korea, between September 1994 and September 2010.

Results: Of the patients with MGC, 101 (2.60%) were positive for LNM. Multivariate analysis, followed by univariate analysis, revealed the following risk factors for LNM in MGC: large tumor size, undifferentiated tumor type, lymphatic invasion, perineural invasion, and associated ulceration in the tumor (hazard ratio 1.25, 7.49, 20.65, 23.45, and 4.07, respectively). Patients without LNM had significantly increased survival and/or recurrence-free survival rates than patients with LNM (188.4/209.8 months vs 169.5/188.0 months; $P = .029/.004$, respectively). Only 3 of 1065 patients (0.3%) who met the absolute indication criteria for ESD had LNM. Of those who met the expanded indication criteria for ESD, 11 of 2678 patients (0.4%) had LNM. LNM also was found in 2 patients who had a differentiated tumor <0.5 cm without ulceration.

Conclusion: The risk for LNM was very low when patients with MGC met the absolute and/or expanded criteria for endoscopic resection, which meant the indication criteria for ESD was safe and acceptable. However, although the risk for LNM is very low, it should not be considered negligible in endoscopic resection. (Gastrointest Endosc 2016;83:896-901.)

Gastric cancer is the fourth most common cancer and the second leading cause of cancer-related death worldwide.[1,2] International incidence rates of gastric cancer vary widely. The highest rates of gastric cancer in the world occur in eastern Asian countries, including Korea and Japan.[3] For several decades, the necessity of regular endoscopic examination as a secondary prevention has been emphasized in both countries because of the high incidence of gastric cancers. For this reason, early detection has increased the volume of early gastric cancer (EGC) reported in these countries, which now account for 40% to 50% of total gastric cancers.[2-4] EGC is defined as gastric cancer, which is limited to the mucosa or submucosa, irrespective of other conditions.[5]

Currently, endoscopic techniques, including EMR and endoscopic submucosal dissection (ESD) have been used for the curative resection of EGCs. However, although endoscopic resection of EGC has the benefit of organ preservation and maintaining quality of life, its use has been controversial because of the potential risk of lymph node metastasis (LNM). Depending on the depth of invasion, EGCs have a 2% to 5% incidence of LNM in mucosal cancer and a 10% to 25% incidence of LNM in submucosal cancer.[2,3] Endoscopic resection is not currently accepted

Abbreviations: EGC, early gastric cancer; ESD, endoscopic submucosal dissection; LNM, lymph node metastasis; MGC, mucosal gastric cancer; NLNM, negative lymph node metastasis.

DISCLOSURE: *All authors disclosed no financial relationships relevant to this publication.*

See CME section; p. 1023.

0016-5107/$36.00
http://dx.doi.org/10.1016/j.gie.2015.08.051

Received April 15, 2015. Accepted August 6, 2015.

Current affiliations: Department of Trauma Surgery, Regional Trauma Center, Gachon Gil Hospital, Incheon (1), Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea (2).

Reprint requests: Professor Jae Moon Bae, MD, PhD, FACS, Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, 50 Irwon-dong, Gangnam-gu, Seoul 135-710, Republic of Korea.

as an adequate treatment for submucosal gastric cancer because of the relatively high rate of LNM, except in limited circumstances with expanded indications.[3,6]

Endoscopic resection of mucosal gastric cancer (MGC) should be carried out in the absence of LNM. Unfortunately, imaging studies, including EUS, CT, and positron emission tomography are inadequate for detecting LNM.[3,7] Therefore, the prediction of LNM in MGC is difficult and is dependent on patient characteristics and the macroscopic and/or histopathologic features of the tumor. Extensive studies have been performed to determine the risk factors of LNM in MGC, but controversy remains because of the small number of cases evaluated and the heterogeneity of the patients. The aim of the present study was to clarify the risk factors of LNM in MGC by performing a large scale, single-institution study. In addition, we attempted to investigate the association of LNM with the indication criteria for ESD.

MATERIALS AND METHODS

A prospectively collected database was analyzed retrospectively for all patients with MGC who underwent a curative surgery at the Samsung Medical Center, Republic of Korea, between September 1994 and September 2010. Total or distal subtotal gastrectomy with D1 + β or greater lymph node dissection[6] was performed depending on the location and macroscopic type of tumor for all patients. A distal subtotal gastrectomy was performed with a tumor-free margin ≥2 cm. The extent of lymph node dissection was determined in accordance with the recommendations of the Japanese Research Society for Gastric Cancer.[6]

The cancers were staged according to the staging manual of the American Joint Committee on Cancer.[8] Curative resection was defined as *R0 resection* as described by the Union for International Cancer Control residual tumor classification.[9] Minor histologic categories of gastric cancer were excluded from the study, including adenosquamous carcinoma, squamous carcinoma, small cell carcinoma, lymphoepithelioma-like carcinoma, hepatoid carcinoma, Paneth cell carcinoma, choriocarcinoma, carcinosarcoma, and parietal cell carcinoma.

All lymph nodes from each specimen were retrieved by palpation under gross inspection without size limitation. Harvested lymph nodes were examined with 4 mm–thick sections along its long axis.

The patient characteristics (age, sex) and the following pathologic factors were compared between the patient group with LNM (LNM group) and without LNM (negative lymph node metastasis [NLNM] group): size and/or depth of invasion (lamina propria vs muscularis mucosa), tumor location (upper/middle/lower third), macroscopic type (I, protruded type; IIa, superficial elevated type; IIb, flat type, IIc; superficial depressed type; III, excavated type),[10] differentiation (a well and/or moderately differentiated adenocarcinoma was considered a differentiated tumor, and a poorly differentiated and/or signet ring cell and/or mucinous carcinoma was considered an undifferentiated tumor), multiplicity of tumor and/or Lauren classification,[11] the presence of ulceration, and the presence of lymphatic and/or vascular and/or perineural invasion.

The absolute indications for endoscopic resection were defined as a differentiated-type adenocarcinoma ≤ 2 cm in diameter without ulcerative findings. Expanded indications for ESD were defined as (1) differentiated tumor > 2 cm in diameter without ulceration, (2) differentiated tumor ≤ 3 cm in diameter with ulceration, and (3) undifferentiated tumor ≤ 2 cm in diameter without ulceration.[6]

Statistical analysis

All continuous data are presented as mean ± standard deviation, unless otherwise noted. Univariate and multivariate analyses were performed. For univariate analysis, the Fisher exact test or χ^2 test was used for nominal and categorical variables and the *t* test was used for continuous variables. Logistic regression analysis was used for multivariate analysis. A P value < .05 (two-tailed) was considered statistically significant. All statistical analyses were performed with SPSS 19.0 for Windows (IBM SPSS Inc, Chicago, Ill).

RESULTS

Of a total of 12,996 patients who underwent radical gastrectomy, 7074 patients (54.4%) were classified as having EGC. Histopathologic examination revealed that 3123 patients (24.0%) had submucosal tumors. A total of 3951 patients with MGC (30.4%) were enrolled in the current study. Among the patients with MGC, 101 (2.60%) had LNM pathologically.

In univariate analysis, the LNM group was significantly younger than the NLNM group (51.1 ± 11.3 vs 54.6 ± 11.7 years, respectively; $P = .002$), and there was a significantly higher incidence of LNM in women than in men (3.4% vs 2.1%, respectively; $P = .016$). The LNM group also had a larger mean tumor size than the NLNM group (4.2 cm ± 2.5 cm vs 2.6 cm ± 1.8 cm, respectively; $P < .001$). The LNM group had significantly more undifferentiated tumors than the NLMN group (89.1% vs 48.1%, respectively; $P < .001$), and, according to the Lauren classification,[11] most LNM tumors were of the diffuse type, whereas most NLNM tumors were of the intestinal type (18.8%, 75.2%, 5.9% vs 54.1%, 43.3%, 2.6% for intestinal and/or diffuse and/or mixed types in LNM and NLNM, respectively; $P < .001$). The LNM group had more frequent microscopic ulceration than the NLNM group (15.8% vs 3.8%, respectively; $P < .001$). Finally, lymphatic invasion and perineural invasion were more frequent in the LNM group than the NLNM group (19.8% vs 1.4%; $P < .001$ and 2.0% vs 0.1%; $P = .006$, respectively) (Table 1).