Considerations in expanding indications for endoscopic treatment of early gastric cancers

(조기위암 내시경치료 적응증 확대의 유의점)

Author: Jun Haeng Lee, M. D. (이준행)

Affiliation of the authors: Jun Haeng Lee, M.D. Department of Medicine, Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul Korea

Correspondence to: Jun Haeng Lee, Division of Gastroenterology, Department of Medicine, Sungkyunkwan University School of Medicine, Samsung Medical Center, Irwon-dong, Gangnam-gu, Seoul, 135-710, Korea
Telephone: +822-3410-3409
E-mail: stomachlee@skku.edu

Introduction

The detection rate of EGC has been steadily increasing in eastern countries ("*EGC epidemic*"). Many factors may have contributed to it. (1) The main reason for this increase might be the widespread use of the endoscopy – especially in individuals with mild or no symptoms. As screening colonoscopy is commonly recommended in western countries, screening upper enoscopy is recommended in Korea. (2) Patients' awareness of the significance of early detection is also an important factor. (3) The accumulated experience of the endoscopists may have increased the detection rate of small gastric cancers. (4) High resolution endoscopies that are available in most institutions may be an contributing factor. However, it is not certain whether sophisticated techniques, such as narrow band imaging (NBI) or auto-fluorescence imaging (AFI) have contributed to this phenomenon. In my view, the willingness of the endoscopist to find an early lesion is the most important factor.

Patients who undergo resection for EGC have an excellent prognosis, with a 5-year survival rate of over 90%.[1,2] In long-term follow up studies for curatively resected EGC patients, more patients usually die from comorbid disease or other secondary cancer than the recurrence of the gastric cancer.[2,3]

However, the quality of life after the conventional surgical resection of gastric cancer is substantially impaired. Therefore, less invasive treatment options for EGC have been developed.[4] EMR is currently accepted as a standard treatment for selected cases with EGC.[5-8] However, this acceptance is not free from skepticism. As a western reviewer put it,[9] appropriate indications and clear guidelines are a prerequisite for a successful outcome and any mistake in this area may result preclude or significantly delay a curative surgical resection and may result fatal for the patients.

Traditional indications of EMR

The ideal candidates for EMR are EGC patients who have no risk of lymph node metastasis. However, it is impossible to select these candidates in clinical practice. The practical alternative is to select lesions for which the risk of lymph node metastasis is nil or lower than the surgical risk.[9] This idea has some limitations: (1) The average technical expertise of the endoscopists – a frequently neglected aspect -- needs to be considered. (2) The surgical risk of radical surgery for the EGC is quite different in various countries. Although standard surgery for gastric cancer is one of the most safe abdominal surgical procedures, the mortality rate is around 0.5-1.0% in eastern countries.[10] This rate was used when selecting patients for with of comparable or fewer risks of lymph node metastasis compared with the mortality associated with surgery. However, the mortality rate for gastrectomy with D2 dissection is about 2-10% in western countries.[11] (3) Although EMR is generally considered to be less aggressive than the open surgery, it is not free from morbidity and mortality. In addition, more recent techniques of EMR, such as ESD, have quite a quite high rate of complication. The cost of ESD is quite high, too. In contrast, the risk of surgical treatment of EGD is getting lower with the introduction of laparoscopic surgery. So the risk and cost of the EMR procedure need to be considered.

With technical advances of EMR, the size of lesion which can be resected en bloc is becoming larger.[6] Care must be given because EMR has a very important limitation that lymph nodes cannot be dissected. The data from Korea and Japan have shown that the incidence of lymph node metastasis in intramucosal EGC was about 2-3% and the risks increase up to 20% when the submucosal invasions are present.[6,12-14] Because results of the long-term controlled trial is not available, the current indications of EMR are based on the detailed analysis of pathology results from surgically resected gastric cancers.

Regarding this issue, inter-observer and/or inter-institutional variation in the pathology report of surgical and EMR specimen may be a great problem.[15] In addition, pathology reports before and after EMR may be different. For example, pathology specimen of EMR for gastric dysplasia in some cases may show gastric cancers.[16] It is important to standardize the pathology report to compare the surgery or EMR results from different institutions. In Korea, the Gastrointestinal Pathology Study Group of the Korean Society of Pathologists developed a standardized reporting format for gastric cancer.[17]

The ideal candidates for EMR are EGC patients who have no risk of lymph node metastasis. The problem is that there is no method which can definitely evaluate the status of lymph node without surgical dissection. Ideally, endoscopic ultrasound (EUS) should be useful for selecting patients without lymph node metastasis. However, clinical studies evaluating the role of EUS before EMR for EGC have shown unsatisfactory results.[18,19] One possible explanation may in the subjective nature of the interpretation of EUS findings. Inter-observer variation, partly due to the personal expertise, seems to be a great limitation of EUS. Some positive results in centers specialized for EUS cannot be expected in the daily clinical practice.

The most conservative but widely accepted indications of EMR for the treatment of EGC are as follows: (1) differentiated (well- and/or moderately differentiated adenocarcinoma and/or papillary carcinoma) type confined to the mucosa; (2) smaller than 2 cm for superficially elevated type lesions; (3) smaller than 1 cm for the flat and depressed type lesions; (4) without ulcer or ulcer scar; and (5) without venous or lymphatic involvement.[6]

Expanded indications of EMR

Recently, based on some clinical observation and surgical data, expanded criteria for EMR have been proposed.[6,20-22] Likewise, in colon EMR, expanded indication is an important issue.[23] Until now, however, there is a paucity of quality data that support expanding indications of gastric EMR. One report whose EMR indications included the EGC lesions as large as 3 cm showed the disease free survival rates of 98% during a median follow-up of 38 months when complete resections were performed.[24] Recent large surgical data from many institutions also provided supporting evidence for expanded criteria. In differentiated mucosal cancer whose size was 3 cm or smaller, no lymph

node metastasis was observed irrespective of the lesion ulceration; in differentiated mucosal cancer without ulceration, no patient had nodal metastasis regardless of tumor size; and, finally, in differentiated minute submucosal cancer (sm1), no nodal metastasis was found if tumor size was no more than 3 cm.[21] It should be emphasized that mucosal cancers larger than 3 cm in diameter showed higher risk of lymph node metastasis in many unrelated studies.[25] In submucosal cancer, the size limitation should be much stricter, because tumor size >= 2 cm was an independent risk factor of lymph node involvement.[26]

In some institutions, EMR for selected cases with undifferentiated type of EGC has been tried.[27] In EGC with undifferentiated histology, the risk of lymph node metastasis was shown to be significantly associated with lymphatic-vascular invasion.[28] However, the same authors mentioned that this pathologic factor was not useful for identifying patients at high risk of lymph node metastasis who should be offered gastrectomy rather rhan endoscopic mucosal resection.[28] This is because lymphatic-vascular involvement, which cannot be confirmed before EMR or surgery, was the only independent predictive risk factor for lymph node metastasis.[28] In a small study from Korea, authors suggested that poorly differentiated EGC confined to the mucosa or with minimal submucosal infiltration (<or= 500 microm) could be considered for curative EMR due to the low risk of LNM.[29] However, these findings should be confirmed in other large scale studies. With the recent technical advancement, endoscopic treatment of recurred gastric cancer after EMR/ESD has also been tried in some institutions.[30] However, a long-term follow-up seems to be necessary to make a firm conclusion.

In a recently published study, 3 out of 278 surgically treated EGC patients had lymph node metastasis.[31] Lymphatic invasion is one of the strongest risk factors for nodal metastasis in gastric cancer. When there is an evidence of lymphatic invasion in endoscopically resected gastric cancer, curative surgical resection with D2 lymph node dissection is usually recommended. However, the diagnosis of lymphatic invasion may be subjective and often inaccurate because of the difficulty of detecting lymphatic vessels with conventional hematoxylin and eosin staining. Using a new immunihistochemical marker of lymphatic endothelium, D2-40, Sako et al[32] showed that the sensitivity of H & E staining is lower than immunohistochemical staining in the detection of lymphatic invasion in surgically resected EGC specimen. This finding raises a

great concern, because immunohistochemical stating is not performed routinely for EMR specimens.

Regarding the indications of EMR for EGC, I have a relatively conservative position because of the following reasons. (1) We have practically no survival data from controlled studies. There are some peer-reviewed articles on the treatment outcomes of EMR for EGC, but most of them are non-controlled, small-sized, single-center, retrospective studies. (2) The efficacy of EMR is highly operator-dependent. Because the technique of EMR is rather complicated, a good result from an institution cannot be extrapolated into other settings. (3) There are so many different methods under the name of EMR. A favorable outcome with one technique may not be reproduced with another EMR method. (4) The pathologists' points of view are greatly different between eastern and western countries. Even in the same country, the inter-observer variation between pathologists is very high. If pathologic interpretation of resected specimen is highly variable, the reliability of data on treatment outcome is inevitably decreased. (5) Indications of EMR are usually recommended by some group of specialists. Many members of the guideline committee are highly experienced endoscopists, so their recommendations are sometimes too much for average-skilled endoscopiests. So, it must be emphasized that the level of technical expertise should be carefully considered in practical settings. (6) Expanding indication into some submucosal cancers has additional problem because histological distinction between sm1 and sm2 in resected specimen is very subjective; and the thickness of resected submucosal layer is not constant.

The thickness of submucosal layer needs some additional comment. It is generally considered that the mid-submucosal layer is cut in EMR. Because there are lots of technical modifications, the depth of resection may be different by the method. In EMR-P, for example, submucosal layer is grasped with a snare and then mixed-current is supplied for cutting. So, it is very difficult to control the depth of invasion. Possible advantage of EMR-P over ESD may be that the thickness of the resected submucosal layer is rather homogenous. In ESD, endoscopists have some control over the resection depth. Most endoscopists favor to cut the lowest submucosal layer if possible. In the real procedure setting, however, it is very difficult to keep the same depth of resection in ESD. In some areas, the depth of invasion may be enough (for example, more than 500 μm). However, the depth of invasion may be

insufficient to guarantee an acceptable vertical resection margin. It is especially true when the resected area is very large. Detailed histological data analysis is required to answer this question.

Future perspectives

Recent data suggest that EMR provides comparable results to surgery for selected cases of EGC. In addition, limitations in EMR have been reducing with the technical advancement. However, to expand the indications of EMR, some efforts need to be made: (1) the more long-term follow-up data are necessary to support the role of EMR for EGCs in standard indications. Multicenter prospective study should be performed in many countries. (2) The technical details of EMR need to be standardized, so that more endoscopists can perform the procedure with acceptable level of technical skills. (3) The standardization of the pathological interpretation of resected specimen is necessary, so that the results from various institutions can be shared and compared. (4) Data about experiences of EMR for EGCs in expanded indications need to be carefully collected and analyzed. With these efforts, EMR will become safer and more reliable methods for EGCs in expanded indications.

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