Endoscopic mucosal resection of early gastric cancer: Experiences in Korea

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Abstract

Endoscopic mucosal resection (EMR) has been established as one of the treatment options for early gastric cancer (EGC). However, there are many uncertain areas such as indications of EMR, best treatment methods, management of complications and follow-up methods after the procedure. Most studies on this topic have been carried out by researchers in Japan. In Korea, gastric cancer is the most common malignant disease, and the second leading cause of cancer death. In these days, EMR for EGC is widely performed in many centers in Korea. In this review, we will provide an overview of the techniques and outcomes of EMR in Korea.

INTRODUCTION

Early gastric cancer (EGC) is defined as gastric carcinoma confined to the mucosa or submucosa regardless of the presence of regional lymph node metastases[1]. The detection rate of EGC has been steadily increasing because of technical advances and awareness of benefit from early diagnosis, especially in eastern countries. Patients who undergo resection for EGC have an excellent prognosis, with a 5-year survival rate of over 90%[2]. However, the quality of life after conventional surgical resection of gastric cancer is substantially impaired. Therefore, less invasive treatment options for EGC have been developed. Endoscopic mucosal resection (EMR) was first introduced as a treatment modality for EGC in 1984. Since then, various accessories and techniques of EMR have been developed. Early data suggest that EMR provides a survival rate of 90% comparable to that of surgery if the technique is applied with the appropriate indication[3,4]. In addition, morbidity and mortality associated with surgery can be avoided and specimens for accurate pathologic staging can be obtained. Therefore, EMR is currently accepted as a standard treatment for selected cases with EGC[5-7]. Most studies on this topic were performed in Japan, where the incidence of early gastric cancer is very high. Recently, experiences of EMR for EGC in other countries are increasingly reported[7-10]. In this review, we will provide an overview of the techniques and outcomes of EMR in Korea.

INDICATIONS OF EMR

With technical advances of EMR, the size of a 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. Data from Korea and Japan have shown that the incidence of lymph node metastasis in intramucosal EGC is about 2%-3% and the risks increase up to 20% when submucosal invasions are present[6,11-13]. Because results of long-term controlled trials are 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[14]. 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[15]. It is important to standardize the pathology report to compare 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[16].

The ideal candidates for EMR are EGC patients who have no risk of lymph node metastasis. The problem is that there is no method that 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[17,18]. 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[19]. This rate was considered when selecting candidates for EMR, because the risk of lymph node metastasis in patients with EMR should be lower than the surgical risk. From analysis of surgical data, patients with EGC who had minimal risk of lymph node metastasis could be identified and indications of EMR could be established. The current 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].

Recently, based on some clinical observation and surgical data, expanded criteria for EMR have been proposed[6,20,21]. One report in which EMR indications included EGC lesions as large as 3 cm showed the disease free survival rates of 98% during a median follow-up of 38 mo when complete resections were performed[4]. Recent large surgical data from Gotoda et al[21] also provided supporting evidence for expanded criteria. In differentiated mucosal cancer which 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. In some institutions, EMR for selected cases with poorly differentiated type of EGC has been tried[22]. However, a long-term follow-up seems to be necessary to make a firm conclusion. With the recent technical advancement, endoscopic treatment of recurred gastric cancer after EMR has also been tried in some institutions[23].

Regarding the indications of EMR for EGC, we have a relatively conservative position for adopting expanded criteria because of the following reasons: (1) long-term outcome data for expanded criteria are still insufficient; (2) distinction between SM1 (upper one-third of the submucosal layer) and SM2 (middle one-third of the submucosal layer) in pathologic specimen is very subjective; and (3) the thickness of resected submucosal layer is not constant.

TECHNIQUES OF EMR

The instruments and methods of EMR in Korea are basically the same as in Japan. The most advanced technique of EMR is endoscopic submucosal dissection (ESD)[24], which is also widely performed in Korea. Detailed description of the technical aspects is out of the scope of this review. However, some comments seem to

be necessary.

The practice of EMR requires application of additional techniques to standard endoscopy. Chromoscopy is important for delineating the border and assessing the depth of the lesion. Most commonly used stain is indigo carmine solution. During the indigo carmine chromoendoscopy before EMR, some additional lesions of a few millimeters may be found. However, most of the additionally detected lesions are non-neoplastic[25]. Therefore, routine chromoendoscopy for normal-looking mucosa seems to be unnecessary. Narrow band imaging (NBI) with magnification is a relatively new technique to evaluate the mucosal surface in detail[26]. However, it is not certain whether application of NBI before EMR helps increase the rate of complete resection.

Ideally, endoscopic ultrasonography (EUS) should be used in order to further ascertain the depth of invasion before EMR. Accuracy of endoscopic ultrasonography for predicting the depth of gastric cancers was reported to be 70%-80%[18,27,28]. This kind of accuracy range cannot be considered to be sensitive enough to select cancers limited in the mucosal layer. In the EUS evaluation of EGC, overstaging of mucosal cancer as submucosal cancer is reported to be quite common[18]. The overstaging can lead to unnecessary surgery which may have a great impact on the patient's quality of life. In contrast, EUS has some limitation in the detection of microinvasion into the submucosal layer. Until now, the use of EUS before EMR seems to be operator-dependent.

The list of EMR methods is quite long[29], but the basic steps are in common: (1) delineation of the lateral margin with or without chromoendoscopy, (2) marking using brief burst of electrocautery or argon plasma coagulation, (3) submucosal injection to lift the lesion, and (4) resection of the lesion. Before the development of ESD, EMR with circumferential precutting (EMR-P) was the best method to cut larger lesions in one piece[30]. Recently, ESD has become the most commonly used method to resect large lesions[31,32]. ESD was originally developed in Japan, but it is also being performed in other parts of the world[10,33,34]. In Japan, the development of ESD was largely based on new devices like IT-knife, Flex-knife, Hook-knife, triangle-tipped knife, and narrow calibered transparent hood. In Korea, new types of knives such as Fixed flexible snare and Endo FK were also developed.

COMPLICATIONS OF EMR

The complications of EMR include pain, bleeding, perforation, and EMR-induced ulcer. Pain after resection is typically mild and dull in nature. Pain can be controlled using a standard dose of proton pump inhibitor (PPI) twice a day with or without analgesics. Bleeding is the most common complication and most bleeding occurs during the procedure or within 24 h[9]. Bleeding can be successfully treated in most cases through coagulation of the bleeding vessels, or placement of metallic clips.

EMR-induced ulcer is reported to heal faster and to recur less often than noniatrogenic gastric ulcer and usually treated with antisecretory agents. One study showed that all ESD-induced ulcers healed within 8 wk regardless of

size and location using standard doses of PPI for 8 wk[35]. However, there is no consensus regarding the duration of PPI therapy for these ulcers. Recently, our institution reported that 1 wk omeprazole therapy is equivalent to 4 wk therapy in terms of EMR-induced ulcer healing rate and ulcer-related symptoms[36]. It is not certain whether administration of anti-acids before EMR reduces the complications of EMR. Watanabe *et al*[37] conducted a randomized clinical study in which EMR was performed with or without 1 wk of preoperative PPI administration. Artificial ulcers created by EMR healed more rapidly in patients who received preoperative PPI. They concluded that preoperative administration of PPI before EMR is useful for controlling and preventing bleeding, and for facilitating the healing of artificial ulcers[37]. Further studies are necessary to determine the optimal medical treatment in terms of selection of drugs, duration of treatment, mode of administration and the necessity of pre-EMR medication.

The rate of perforation by EMR is about 1%-7%[5,38]. Immediately recognized small perforations can be successfully treated non-surgically with a combination of endoscopic clipping, nasogastric suction, and broad-spectrum antibiotics[38]. Large perforations require immediate surgery. However, management of patients with microperforation (case with free air on chest X-ray after EMR without recognizing perforation during the procedure) is not well established. In our institution, we experienced 13 cases of microperforations during last two and a half years[39]. Among them, 11 cases were successfully treated only with fasting, nasogastric tube drainage, and broad-spectrum antibiotics. About two thirds of the patients with microperforation (7/11) experienced abdominal pain that required short-term intermittent intravenous analgesics. No additional endoscopic treatment was needed[39]. In order to detect microperforation, we recommend to check chest X-ray immediately after EMR.

ADDITIONAL TREATMENT AFTER EMR

Histological examination after EMR is very important to determine the completeness of resection. Radical surgery or additional endoscopic treatment may be recommended for patients with incomplete resection.

Histologically, positive resection margin can be divided into two types; positive lateral resection margin and positive vertical resection margin. If only the lateral margin is positive, additional endoscopic treatment may be tried. However, great care must be given to the positive vertical resection margin. When the vertical margin is positive for malignant cells, the depth of invasion cannot be determined. In EMR, the depth of resection is usually the mid-submucosal layer. So, the positive vertical resection margin usually means that the depth of tumor invasion is SM2 or more. Chung *et al*[40] reported their result of surgery after incomplete endoscopic resection for EGC. In 10 patients with positive resection margin in EMR specimens, there were 2 cases with lymph node metastasis[40]. In our opinion, radical surgery is mandatory when the vertical resection margin of the EMR specimen is positive.

EMR is usually attempted when the cancer is thought to be limited to the mucosal layer. However, about 10%-20% of EMR specimens show evidence of submucosal invasion[4]. There is no consensus on the necessity of additional surgery for these cases. The safest way is to do radical surgery in every patient with submucosal invasion. However, careful observation is a possible option for cases with minute submucosal invasion in SM1 layer with negative vertical margin[5]. The cutoff value of minute submucosal invasion in SM1 layer is usually 500 μm. Recently, Cho *et al*[41] raised a concern about this cutoff value. When a 2 cm × 2 cm piece of porcine gastric wall was stretched into 3 cm × 3 cm, the thickness of submucosal layer decreased from 500 μm to 200 μm. This was exactly the same in the human gastric mucosa. When a 2.5 cm × 1.0 cm piece of human gastric antral wall was stretched into 3.0 cm × 1.0 cm, the depth of submucosa decreased from 620-650 μm to 250-300 μm[41].

OUTCOMES OF EMR

The best way of evaluating the efficacy of a new treatment is a long-term, large-scaled randomized controlled trial. However, the excellent prognosis after surgical treatment (especially in cases indicated for EMR) makes controlled trial almost impossible. So, the best feasible evidence of the efficacy of EMR is a long-term clinical follow-up data.

Earlier experiences of EMR for EGC from 12 major institutions in Japan were reported by Kojima *et al*[42] in 1998. The lift-and-cut, EMR using a cap (EMR-C), and EMR with ligation (EMR-L) techniques were most commonly used. En bloc resection rate was 75.8%, and complete resection rate was 73.9%. The follow-up period was from 4 mo to 11 years. Recurrence rate after histopathologically documented eradication was 1.9% and recurred lesions were treated with endoscopic retreatment or surgery. The disease-specific survival rate was 99.1%.

The most commonly referenced result of endoscopic mucosal resection of EMR was published in 2001 by Ono[4]. Four hundred and seventy nine cancers in 445 patients were treated by EMR from 1987 to 1998, but submucosal invasion was found on subsequent pathological examination in 74 tumors. Sixty nine percent of intramucosal cancers (278/405) were resected with a clear margin. Local recurrence in the stomach occurred in 17 lesions followed conservatively, in one lesion treated endoscopically, and in five lesions with complete resection. There were no gastric cancer related deaths during a median follow up period of 38 (3-120) mo[4].

Recently, Oda *et al*[43] reported the outcomes of ESD for EGC using IT knife, which was superior to that of other conventional methods. They used expanded criteria, suggested by Gotoda *et al*[5,6] as mentioned above. *En bloc* resection rate was up to 98%, and complete resection rate was 83%[43].

In Korea, a multi-center, retrospective study has been performed[34]. From January 2000 to December 2002, 514 EGCs in 506 patients were treated by EMR in 13 institutions. The most commonly used technique was circumferential precutting followed by snare resection

(EMR-P, n = 269, 52.3%). Complete resection and incomplete resection after EMR were confirmed in 399 lesions (77.6%) and 103 lesions (20.0%), respectively. For completely resected mucosal cancers (n = 399), the median duration of follow-up was 23.5 (range, 5-70) mo. In this group, local recurrence was detected in 24 cases (6.0%) with a median interval between EMR and recurrence of 17.9 (range, 3.5-51.7) mo. There were 3 cases with perforation and 71 cases with bleeding. There was no death related with recurrence of gastric cancer during the overall median follow-up period of 39 mo[34].

In our institution, 283 patients with EGC have been treated by EMR from January 2000 to June 2005[39]. The median age of the patients was 64 (range 26-85) years. The male to female ratio was 3.2:1. The methods of EMR were mainly snare resection after circumferential precutting (EMR-P, n = 162) and ESD (n = 91). The criteria for curative resection were en bloc resection or complete resection in piecemeal resection, well or moderately differentiated histology, free of tumor in resected margin, intramucosal lesion, and no vascular or lymphatic invasion. Additional treatments, usually surgery, were recommended for cases with non-curative or non-evaluable results. The median duration of follow-up was 21 (range 3-66) mo. The mean size of cancerous lesion was 1.38 cm. The overall rate of curative resection was 72.1%. The rate of curative resection was highest with ESD (80.2%), followed by EMR-P (70.3%). Submucosal invasion was found in 44 cases (15.5%). In patients with curative resection, local recurrence at EMR site was found in only one case (0.5%). In 51 cases who underwent surgical resection due to non-curative or non-evaluable resection, residual cancer was found in 13 cases (25.0%). Among 28 patients, who were followed up without surgery after non-curative or non-evaluable results, there were 13 recurrences (12 local recurrences and 1 hepatic metastasis) after a median follow-up of 7 mo. Five patients died during the follow-up period, but there was no death related to gastric cancer[39].

Jung et al[44] showed comparable results to ours. In that study, 341 EGC patients were treated by EMR-P. Complete resection rate was 84.5%. During 47 mo of follow-up, 1.4% of patients underwent recurrence after complete resection. Recurrence rate after incomplete or non-evaluable resection without additional treatment was 9.1%. The median duration between EMR and local recurrence was 21 mo. The overall 5-year survival rate after EMR was 90% and no death from gastric cancer occurred during follow-up[44].

Rye et al[45] reported their follow-up results after EMR for gastric adenoma or EGC. More than 80% of cases were treated with endoscopic incision and submucosal dissection (EISD). The recurrence rate was 9.6% (4/41) in patients treated with conventional EMR, and 3.5% (8/230) in patients treated with EISD[45].

Lee et al[41] reported a prospective randomized controlled trial of EMR evaluating the efficacy of a fibrinogen mixture as a submucosal injection solution. No significant differences were observed between the 2 groups (the fibrinogen mixture group versus the normal saline group) in the rates of en bloc resection (80.6% vs 88.9%), complete resection rate (86.1% vs 80.6%), and recurrence rate (3% vs 6.1%)[41].

Youn et al[46] reported their clinical outcomes of EMR for EGC. The overall complete resection rate was 84.6% (126/149) while complete resection rate of 93.5% was achieved in mucosal cancers (115/123). The success of complete resection was significantly affected by endoscopic gross type (depressed lesion), the degree of differentiation, and the depth of invasion, independently. There were 5 cases of local recurrence with no disease-related or treatment-related mortality during the follow-up period[46].

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 treat more EGCs with EMR, some efforts need to be made: (1) More long-term follow-up data are necessary to support the role of EMR in EGC treatment. Multicenter prospective studies should be performed in many countries. (2) The technical details of EMR need to be standardized, so that more endoscopists can perform EMR with an acceptable level of technical skills. Teaching systems by experts may help trainees to challenge EMR more easily; (3) Standardization of the pathological interpretation of resected specimen is necessary, so that the results from various institutions can be shared and compared. With these efforts, EMR will become safer and more reliable methods for EGC treatment.

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