Success rate of curative endoscopic mucosal resection with circumferential mucosal incision assisted by submucosal injection of sodium hyaluronate

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Background: Circumferential mucosal incision around a lesion is effective for reliable endoscopic mucosal resection. However, mucosal incision with a needle knife is difficult, even with submucosal injection of normal saline solution. To make needle-knife incision easier and safer, sodium hyaluronate has been used instead of normal saline solution. The aim of this study was to evaluate the clinical outcome of endoscopic mucosal resection with circumferential mucosal incision assisted by submucosal injection of sodium hyaluronate.

Methods: For 70 gastric lesions treated by submucosal injection of sodium hyaluronate, the size of the lesion and the resection specimen, the en bloc resection rate, complications, and local recurrence during follow-up were assessed.

Results: The mean size of the lesions and resection specimens were, respectively, 19.9 mm and 30.0 mm. The en bloc resection rates were 89% (42/47) for lesions up to 20 mm in diameter and 48% (11/23) for those greater than 20 mm (1-20 mm vs. >20 mm, \( p = 0.0004 \)). Three patients underwent surgery because of invasive cancer in the EMR specimen. During follow-up (median 14 months, range 3-38 months), 2 recurrent lesions were found. No major complication occurred.

Conclusions: Submucosal injection of sodium hyaluronate is a reliable method with a high success rate for en bloc resection of lesions up to 20 mm in diameter. Mucosal incision with a needle knife can be performed safely with submucosal injection of sodium hyaluronate. (Gastrointest Endosc 2002;56:507-12.)

Endoscopic mucosal resection (EMR) is widely used for removal of nonpolyoid early stage neoplastic lesions of GI tract.\(^1\)\(^2\) Frequently used EMR techniques for intramucosal gastric tumors include strip-biopsy and endoscopic mucosal resection with a cap-fitted endoscope (EMR-C).\(^2\)\(^3\) However, with these conventional techniques, the size of the specimen obtained in a one-piece resection is limited (approximately 10-15 mm on average). Therefore, for en bloc resection, these techniques are only reliable for lesions 10 mm or less in size.\(^2\)\(^5\)

Circumferential mucosal incision around a lesion before snaring effectively enhances the outcome of EMR.\(^6\) However, mucosal incision with a needle knife is considered difficult, with a substantial risk of perforation, even with prior submucosal injection of normal saline solution. To make mucosal incision with a needle knife easier and safer, sodium hyaluronate can be used instead of normal saline solution for submucosal injection. In studies with porcine stomachs and dogs, mucosal elevations created by submucosal injections of sodium hyaluronate persisted for longer periods of time and produced clearer margins compared with elevations produced by injection of normal saline solution.\(^7\)

Persistence of the mucosal elevation makes mucosal incision with a needle knife easier and safer by reducing the risk of unintended incision of the muscularis propria and by reducing the number of injections and procedure time. Based on the results of the animal studies, this technique was applied clinically beginning in June 1998.\(^8\) This study evaluates the clinical outcome of EMR with circumferential mucosal incision assisted by submucosal injection of sodium hyaluronate (EMRSH).

PATIENTS AND METHODS

EMRSH was performed for 70 early stage neoplastic lesions of the stomach between June 1998 and April 2001. Use of EMRSH was approved by the ethical committee of our medical school, and written informed consent was obtained from all patients. The mean age of the 70
patients (55 men, 15 women) was 70.1 years (range 48-85 years); follow-up ranged from 3 to 38 months (median 14 months). Indications for curative EMR were (1) well or moderately differentiated adenocarcinoma or adenoma, (2) absence of ulceration, and (3) no findings of invasion apparent. Lesion size was not an exclusion criterion. However, some patients with ulcerated, submucosally invasive, and/or poorly differentiated lesions were treated by EMR because of comorbid conditions, such as concomitant unresectable malignancy, that made them unsuitable as candidates for surgery. Depth of invasion was assessed by endoscopic appearance and EUS with a 20 MHz through-the-scope EUS catheter probe (UM-2R; Olympus Optical Co. Ltd., Tokyo, Japan) before EMR. By endoscopic appearance, superficially protruded lesions with a smooth surface and lesions with shallow depressions but without bank formation or an uneven surface were considered mucosal. Findings that suggest submucosal invasion include lesions with a rigid base, irregularly shaped nodules on the margin, and/or interrupted and enlarged converging folds. Ulcerative lesions surrounded by a tumorous bank and those with folds that were elevated and merged were considered advanced-stage cancers. At EUS, if the hyperechoic layer corresponding to the submucosa was intact, the tumor was judged to be resectable by EMR. If this sonographic layer was destroyed by a hypoechoic tumor arising from the hypoechoic mucosal layer, massive invasion of the submucosal layer or deeper was considered to be present, indicating that the tumor was unresectable by EMR. During the study period, all gastric lesions suitable for EMR were treated by EMRSH. Because submucosal invasion and/or vessel involvement are associated with high risks of lymph node involvement and distant metastasis, surgical intervention was strongly recommended when histopathologic evaluation of the resection specimen revealed such findings.

Patients were prospectively followed and endoscopy was performed at 3, 6, and 12 months after EMR during the first year and yearly thereafter to look for local recurrence. The size of the lesions and the overall size of the resection specimens were determined by direct measurement. For lesions resected piecemeal, size was determined by measurement after reconstruction of the specimens. The resection specimens were examined histopathologically to determine the histopathologic type of the lesion, depth of invasion, and completeness of resection. The specimens were sectioned into 2-mm slices. Complete resection with negative margin was defined as absence of neoplastic change (nonneoplastic glands observed between margin of the tumor and cut margin) in the first and last slices of the specimen. When the neoplastic change was present in any margin of the slices, the specimen was defined as incomplete with a positive margin. The status of the resection margin was considered undetermined when it could not be identified because of piecemeal resection or improper sectioning of the specimen.

EMR was performed with a standard, single-accessory channel endoscope without an elevator (GIF-Q230 or GIF-Q240; Olympus) with the patient under conscious sedation with a combination of intravenously administered midazolam or diazepam and meperidine. EMRSH is performed as follows (Fig. 1). After confirming the margin of the neoplasm, marking dots for the incision were placed about 5 mm outside the margin with a needle knife (KD-10Q-1, Olympus) and an electrosurgical unit (UES-10, Olympus) set at 2.5 for coagulation current (approximate-

To elevate the mucosa along the line of incision, a solution of 0.5% sodium hyaluronate with 0.001% epinephrine and 0.004% Indigo carmine dye was injected with a 21-gauge needle into the submucosa with a 5-mL syringe. The 0.5% sodium hyaluronate solution was made by mixing 1.0% sodium hyaluronate (Artz 1%, Kaken Pharmaceutical Co., Tokyo, Japan; average molecular weight, 800,000 d; derivative type, rooster comb) with the same volume of normal saline solution. The injections were started at the most distant margin of the tumor. The mucosa was incised to the muscularis mucosa along the line at the most distant margin of the tumor. Because the line of incision is elevated by the submucosal injections, incision with a needle knife can be performed safely and easily, even at the most distant edge of the tumor. A cylindrical transparent hood, attached to the endoscope to maintain a satisfactory view during the procedure. It is also useful to control the depth of the incision by controlling the length of the needle knife beyond the edge of the hood. The incision was made with an electrosurgical generator output setting of 3.5 (approximately 40 W) and blended current. After completing the

Figure 2. A, Endoscopic view of superficial elevated (type IIa) early stage gastric cancer on lesser curvature of angulus with marking dots around lesion after spraying with Indigo carmine dye. B, Lesion separated from surrounding mucosa by circumferential mucosal incision along marking spots (a cylindrical transparent hood was attached to the endoscope to maintain a satisfactory view during the procedure). C, Region after EMR. D, Resection specimen (52 × 32 mm). E, Photomicrograph of resection specimen showing intramucosal, well differentiated tubular adenocarcinoma with a clear surgical margin (H&E, orig. mag. ×3). F, Photomicrograph of tumor margin (H&E, orig. mag. ×20).
incision at the distant margin, sodium hyaluronate solution was injected at the lateral side of the tumor, the incision then being extended laterally. As a final step, the incision procedure was repeated for the closest side of the tumor. When the circumferential incision is completed, the mucosal elevation created by local injections of the sodium hyaluronate solution forms a bank around the tumor. To cause the tumor to protrude, an additional submucosal injection of sodium hyaluronate solution or normal saline solution was made at the center of the tumor. A polypectomy snare was then placed along the incision line and tightened, and then endoscopic resection was performed (setting 3.5 to 4.5, blended and/or cutting current; approximately 40 to 80 W). Tumors are usually resected in a single piece with this method (Fig. 2). The entire procedure usually required 30 to 60 minutes.

For statistical analysis of the data, a contingency table chi-square test for independence and the Fisher exact probability test were used, as appropriate.

RESULTS

Seventy early stage neoplastic lesions of the stomach in 66 patients were treated by EMRSH during the study period of 35 months. Five lesions in 5 patients (4 with ulceration scars and 1 poorly differentiated type with submucosal invasion) were treated without curative intent. The early stage lesions consisted of 56 adenocarcinomas and 14 adenomas. Mean size of the lesions was 19.9 mm (5-60 mm); the mean size of the resection specimens was 30.0 mm (15-73 mm). The en bloc resection rate and histopathologic margin data by size of tumor are shown in Table 1. The overall rate of successful en bloc resection was 76% (53/70). The rate was 100% (15/15) for lesions up to 10 mm in size and 84% (27/32) for those between 11 mm and 20 mm. The en bloc resection rate was significantly lower (48%; 11/23) for lesions exceeding 20 mm in diameter (1-10 mm vs. >20 mm, \( p = 0.0008 \); 11-20 mm vs. >20 mm, \( p = 0.007 \)). The en bloc resection rate was unrelated to lesion location.

Histopathologic evaluation confirmed complete resection (negative margin) in 77% (54/70) of all cases, 87% (46/53) of lesions resected en bloc and 47% (8/17) of lesions resected piecemeal. The rates of complete resection for lesions up to 10 mm in size, between 11 and 20 mm, and over 20 mm were, respectively, 87% (13/15), 78% (25/32), and 70% (16/23). The resection margin was positive in 2.9% (2/70). In one patient, the deep margin was considered positive because of submucosal invasion of the carcinoma, and he underwent additional open surgery. In the other patient, the lesion was a diffuse laterally spreading intramucosal carcinoma without a clear endoscopic border and resulted in a positive resection margin. This patient was followed after additional endoscopic ablative therapy with argon plasma coagulation. In 20% (14/70) of the cases, margin status was regarded as undetermined, mainly because of piecemeal resection. Submucosal invasion was found in 8 cases. Of these patients, 5 had only minute submucosal invasion (<500 \( \mu \)m in depth) and 3 had apparent invasion (>500 \( \mu \)m in depth). Four patients with minute invasion were followed without additional therapy. One patient with minute invasion and 2 with apparent invasion underwent gastrectomy with D2 lymph node dissection. Histopathologic examination of the surgical specimens did not reveal residual neoplasm in these 3 patients after surgery. One patient with apparent submucosal invasion by poorly differentiated adenocarcinoma (resection margin negative) was followed without additional surgery because of concomitant incurable hepatocellular carcinoma. Among the 67 lesions in 63 patients who did not undergo additional surgery, 2 (3%) had local recurrence during follow-up. In both cases, the lesions had been resected piecemeal. One patient with a recurrence was followed without additional therapy because the recurrent lesion was a benign adenoma. The other recurrent lesion was a well-differentiated adenocarcinoma found 1 year after the initial EMR. It was treated with further en bloc EMRSH that resulted in a complete resection. There was no recurrence among patients who underwent en bloc resection, and none

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<th>Table 1. Rates of en bloc resection and pathologic margins with EMRSH, according to lesion size</th>
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<td>Size, mm</td>
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<td>% (No.)</td>
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<td>En bloc resection*</td>
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<td>Pathological margin†</td>
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*Size 1-10 mm vs. 11-20 mm, \( p = 0.16 \); size 1-10 mm vs. >20 mm, \( p = 0.0008 \); size 11-20 mm vs. >20 mm, \( p = 0.007 \).
†Not significant, \( p = 0.46 \).
Endoscopic mucosal resection with sodium hyaluronate  


with the patient followed 15 months after resection of a poorly differentiated cancer with apparent submu-
cosal invasion.

Bleeding occurred in 4% (3/70) of cases after the 
procedure. One episode developed during the same 
day as the EMRSH and was treated by endoscopic 
application of hemoclips. The other episodes 
ocURRED 1 day after EMRSH in 1 case and 3 days 
later in the other. Both episodes were managed by 
endoscopic local injection of hypertonic saline and 
epinephrine solutions. All 3 patients were also treat-
ed by intravenous administration of an H2-receptor 
antagonist. Neither blood transfusion nor surgery 
were required for any patient. No other complica-
tion, such as perforation, was noted. Patients did not 
complain of significant symptoms such as abdomi-
nal pain, nausea, or anorexia after EMRSH. The 
average volume of sodium hyaluronate solution 
used in each case was 18 mL.

DISCUSSION

EMR is widely accepted as a standard treatment 
for early stage neoplastic lesions of GI tract includ-
ing intramucosal carcinoma and benign tumors with 
malignant potential. Although EMR is beneficial 
because it is much less invasive than open surgery, 
the indication for this technique should be carefully 
evaluated because some lesions are only curable 
with open surgery. EMR with curative intent is indi-
cated for lesions with minimum risk of lymph node 
involvement. Strict inclusion criteria for curative 
EMR have been established for early stage gastric 
cancer: well-differentiated adenocarcinoma, less 
than 20 mm in diameter, and tumor invasion limited 
to the mucosa without ulcer (scar). However, in 
recent years the possibility of expanding the indica-
tions for EMR has been suggested. Our belief is 
that larger, superficial, and differentiated-type gas-
tric cancers without ulceration or scar can be treated 
locally as long as invasion is limited to the mucosa.

The biggest advantage of EMR over other endo-
scopic local therapies, such as laser photocoagu-
atlon, electrocoagulation, and cryotherapy, is the capability 
to retrieve the resection specimen, which in turn 
ensures histopathologic examination. Complexity of 
local resection can be determined by histopathologic 
examination of the retrieved specimen. If this shows 
submucosal invasion and/or vessel involvement, 
which indicate a high risk of lymph node involve-
ment, additional surgical intervention should be 
strongly recommended. However, this advantage is 
diminished by piecemeal EMR because accurate 
rerangement of the multiple pieces of the specimen 
is sometimes impossible. Moreover, a higher rate of 
local recurrence has been reported with piecemeal 
compared with en bloc resection. Therefore en bloc 
EMR is desirable whenever possible, and for this pur-
pose a new method of EMR was developed with a vis-
cous substance, sodium hyaluronate.7,8

Because the sodium hyaluronate solution is thick 
and viscous, local injection creates a more promi-
lent and longer-lasting mucosal protrusion than normal saline solution.7 Even after incision of the 
mucosa, the injected sodium hyaluronate solution 
does not flow out from the submucosal layer in con-
trast to normal saline solution. Therefore, incision 
around the tumor can be performed safely with sodi-
um hyaluronate.8 The circumferential incision tech-
nique used in the present study results in a higher 
rate of en bloc resection. Even if resection is piec-
meal with this method, the risk of residual neo-
plasm can be minimized by ensuring complete resec-
tion of the mucosa within the circumferential incision. In addition, the method does not require a 
therapeutic endoscope and can be performed with a 
standard, single-accessory channel instrument.

The sodium hyaluronate solution used in the 
present study is isotonic despite its high viscosity. 
Unlike hypertonic solutions, such as hypertonic 
saline solution or 50% glucose, the solution does not 
damage surrounding tissue. This is beneficial with 
regard to safety and results in rapid healing of the 
ulcer created by the resection.

An en bloc resection rate of 100% was achieved in 
the present study for lesions less than 10 mm in 
diameter and was 84% (27/32) for those 11 to 20 
mm. Ono et al.11 reported rates with conventional 
EMR techniques, such as strip-biopsy, for early 
stage gastric cancer of 81% (179/221) for lesions less 
than 10 mm and 57% (81/141) for those between 11 
and 20 mm. They and another group have published 
experience with EMR by using an insulation-tipped 
diathermic knife (IT knife).4,10,11 A circumferential 
mucosal incision was made with the IT knife around 
lesions before snaring. The en bloc resection rates 
with IT-EMR for gastric mucosal tumors were 
reported to be 82% (14/17), 75% (12/16) and 14% 
(1/7) for lesions, respectively, 1 to 10 mm, 11 to 20 
mm and over 20 mm in size.4 Saline with epineph-
rine solution was used for submucosal injection. In 
the method used in the present study, snaring of the 
entire lesion was ensured by the longer-lasting pro-
trusion of the targeted mucosa created by the local 
injection of sodium hyaluronate. However, as also 
noted by Ohkuwa et al.,4 the results of the present 
study also suggest that snaring a lesion greater 
than 20 mm in size is still difficult, even after suc-
cessful circumferential incision. Even with EMRSH, 
the en bloc resection rate falls to 48% when lesions 
reach 20 mm. Although this figure could be consid-
ered fairly good for large lesions, including those as large as 60 mm, it is still unsatisfactory.

Complication rates with respect to bleeding and perforation with IT-EMR were, respectively, 22% and 5%. In addition, the IT-EMR procedure was abandoned in 7% of cases because of complications. In the present study, there was no perforation and the rate of EMRSH-related bleeding was only 4%. None of the patients in whom bleeding occurred underwent surgery, and the EMR procedure was completed in all attempts. The low complication rate in the present study demonstrates that the mucosal incision can be performed safely with a conventional needle knife when sodium hyaluronate is used for submucosal injection. The safety of the mucosal incision is due to the effect of sodium hyaluronate, which creates a more prominent and longer-lasting mucosal elevation. The low rate of postprocedure bleeding could also be due to mechanical compression by the viscous sodium hyaluronate solution and/or the hemostatic effect of epinephrine in the solution, which persists at the resection site for a longer period of time.

During follow-up (median 14 months; range 3-38 months), only 2 recurrent lesions were found among the 67 lesions in 63 patients who underwent EMRSH without additional surgery. Both occurred in patients who underwent piecemeal EMRSH; there were no recurrent lesions after en bloc EMRSH. Therefore, en bloc resection by EMRSH is a reliable method with an extremely low rate of local recurrence. It is our belief that this low recurrence rate was achieved by taking a sufficient margin around lesions. On average, the size of the resected mucosa was about 10 mm larger than that of the lesion itself (30 mm vs. 19.9 mm).

Although there are no comparison studies of the different EMR techniques and long-term follow-up data are needed to validate this form of treatment, the results of the present study indicate that EMRSH is a safe and reliable method for treatment of superficial neoplastic lesions of stomach up to 20 mm in diameter. For en bloc resection of larger lesions, further methodologic improvements would be necessary, such as development of a new cutting technique of submucosal tissue.

**DISCLOSURE**

The primary investigator holds a patent entitled “Method of endoscopic mucosal resection using mucopolysacharide and local injection preparation” filed on May 16, 2000 (United States Patent number 09,570,515).

**REFERENCES**