

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

Hironori Yamamoto, MD, Hiroshi Kawata, MD, Keijiro Sunada, MD, Kiichi Satoh, MD, Yoshinari Kaneko, MD, Kenichi Ido, MD, Kentaro Sugano, MD

Tochigi, Japan

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 rather than 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 nonpolypoid 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

Received September 24, 2001. For revision December 12, 2001. Accepted March 15, 2002.

Current affiliations: Department of Gastroenterology, Jichi Medical School, Tochigi, Japan.

Presented in part at the annual meeting of the American Society for Gastrointestinal Endoscopy, May 20-23, 2001, Atlanta, Georgia (Gastrointest Endosc 2001;53:AB131).

Reprint requests: Hironori Yamamoto, MD, Department of Gastroenterology, Jichi Medical School, Yakushiji, Minamikawachi, Tochigi, Japan 329-0498.

Copyright © 2002 by the American Society for Gastrointestinal Endoscopy 0016-5107/2002/\$35.00 + 0 37/1/128108

doi:10.1067/mge.2002.128108

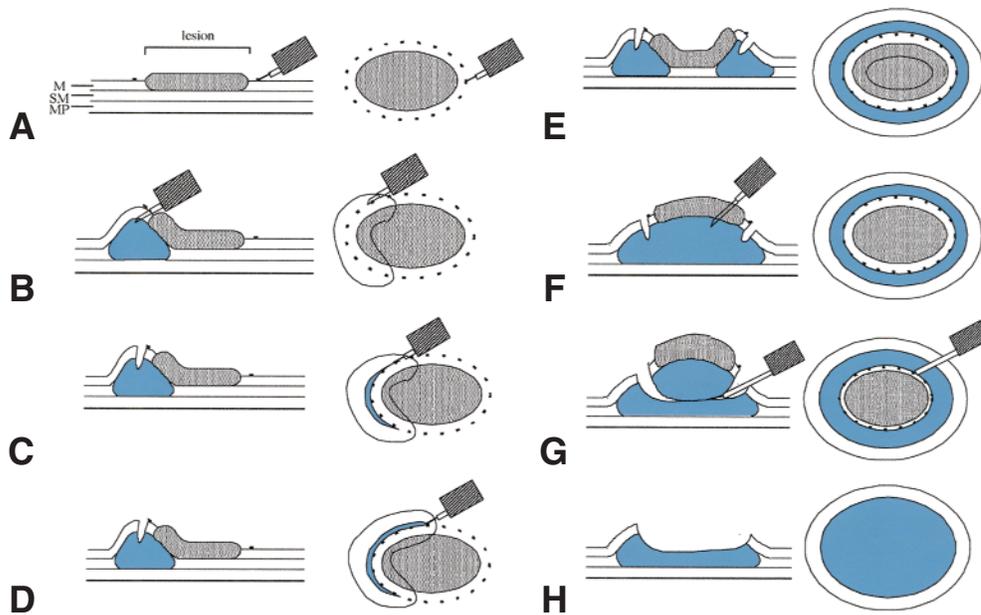


Figure 1. Schematic representation of EMRSH. **A**, Placement of markings for incision line. **B**, Submucosal injections of sodium hyaluronate at most distant margin. **C**, Initiation of mucosal incision at most distant margin. **D**, Extension of incision to lateral side. **E**, Circumferential incision around tumor. **F**, Submucosal injection at center of tumor. **G**, Snaring of tumor. **H**, Complete resection of tumor in one piece (*M*, Mucosa; *SM*, submucosa; *MP*, muscularis propria).

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 electrocautery unit (UES-10, Olympus) set at 2.5 for coagulation current (approximate-

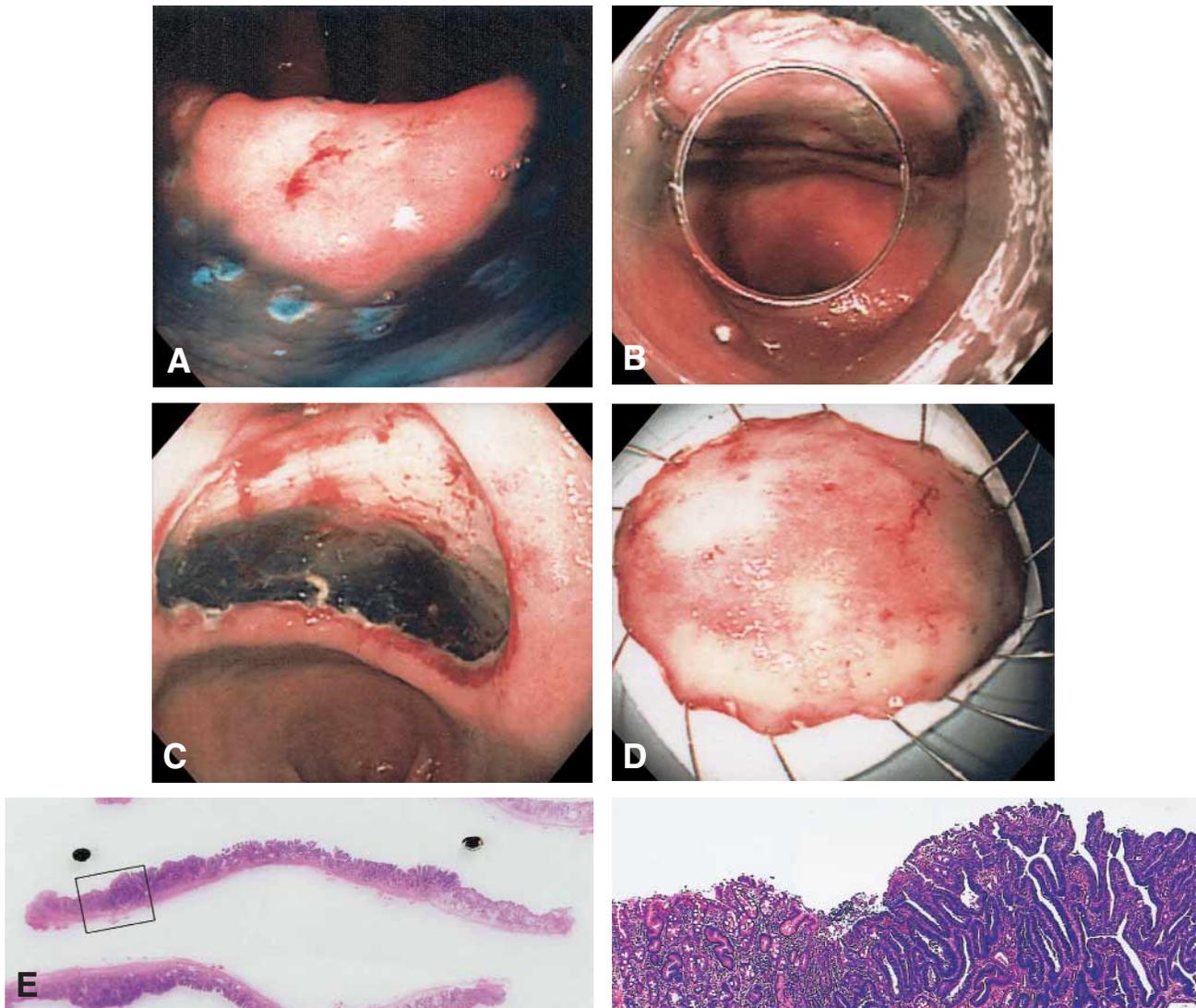


Figure 2. **A**, Endoscopic view of superficial elevated (type IIa) early stage gastric cancer on lesser curvature of angulus with marking dots around lesion after spraying with Indigo carmine dye. **B**, Lesion separated from surrounding mucosa by circumferential mucosal incision along marking spots (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).

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).

ly 20 W). 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 tip, was sometimes used 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

Table 1. Rates of en bloc resection and pathologic margins with EMRSH, according to lesion size

	Size, mm			Total % (No.)
	1-10 % (No.)	11-20 % (No.)	>20 % (No.)	
En bloc resection*	100 (15/15)	84 (27/32)	48 (11/23)	76 (53/70)
Pathological margin†				
Negative	87 (13/15)	78 (25/32)	70 (16/23)	77 (54/70)
Undetermined	13 (2/15)	19 (6/32)	26 (6/23)	20 (14/70)
Positive	0 (0/15)	3 (1/32)	4 (1/23)	3 (2/70)

*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, $p = 0.46$.

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 μ m in depth) and 3 had apparent invasion (>500 μ 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

with the patient followed 15 months after resection of a poorly differentiated cancer with apparent submucosal 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 occurred 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 treated by intravenous administration of an H₂-receptor antagonist. Neither blood transfusion nor surgery were required for any patient. No other complication, such as perforation, was noted. Patients did not complain of significant symptoms such as abdominal 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 including intramucosal carcinoma and benign tumors with malignant potential.² 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 indicated 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 indications for EMR has been suggested.^{9,10} Our belief is that larger, superficial, and differentiated-type gastric 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 endoscopic local therapies, such as laser photocoagulation, electrocoagulation, and cryotherapy, is the capability to retrieve the resection specimen, which in turn enables histopathologic examination.² 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 involvement, additional surgical intervention should be strongly recommended. However, this advantage is diminished by piecemeal EMR because accurate rearrangement 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.⁵ Therefore en bloc EMR is desirable whenever possible, and for this purpose a new method of EMR was developed with a viscous substance, sodium hyaluronate.^{7,8}

Because the sodium hyaluronate solution is thick and viscous, local injection creates a more prominent 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 contrast to normal saline solution. Therefore, incision around the tumor can be performed safely with sodium hyaluronate.⁸ The circumferential incision technique used in the present study results in a higher rate of en bloc resection. Even if resection is piecemeal with this method, the risk of residual neoplasm can be minimized by ensuring complete resection 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.⁷ 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 epinephrine 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 protrusion 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 successful circumferential incision. Even with EMRSH, the en bloc resection rate falls to 48% when lesions exceed 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.⁴ 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 mucopolysaccharide and local injection preparation" filed on May 16, 2000 (United States Patent number 09,570,515).

REFERENCES

1. Takekoshi T, Baba Y, Ota H, Kato Y, Yanagisawa A, Takagi K, et al. Endoscopic resection of early gastric carcinoma: results of a retrospective analysis of 308 cases. *Endoscopy* 1994;26:352-8.
2. Inoue H, Takeshita K, Hori H, Muraoka Y, Yoneshima H, Endo M. Endoscopic mucosal resection with a cap-fitted panendoscope for esophagus, stomach, and colon mucosal lesions. *Gastrointest Endosc* 1993;39:58-62.
3. Tada M, Shimada M, Murakami F. Development of the strip-off biopsy. *Gastroenterol Endosc* 1984;26:833-9.
4. Ohkuwa M, Hosokawa K, Boku N, Ohtu A, Tajiri H, Yoshida S. New endoscopic treatment for intramucosal gastric tumors using an insulated-tip diathermic knife. *Endoscopy* 2001;33:221-6.
5. Matsushita M, Hajiro K, Okazaki K, Takakuwa H. Endoscopic mucosal resection of gastric tumors located in the lesser curvature of the upper third of the stomach. *Gastrointest Endosc* 1997;45:512-5.
6. Hirao M, Masuda K, Asanuma T, Naka H, Noda K, Matsuura K, et al. Endoscopic resection of early gastric cancer and other tumors with local injection of hypertonic saline-epinephrine. *Gastrointest Endosc* 1988;34:264-9.
7. Yamamoto H, Yube T, Isoda N, Sato Y, Sekine Y, Higashizawa T, et al. A novel method of endoscopic mucosal resection using sodium hyaluronate. *Gastrointest Endosc* 1999;50:251-6.
8. Yamamoto H, Koiwai H, Yube T, Isoda N, Sato Y, Sekine Y, et al. A successful single-step endoscopic resection of a 40 millimeter flat-elevated tumor in the rectum: endoscopic mucosal resection using sodium hyaluronate. *Gastrointest Endosc* 1999;50:701-4.
9. Amano Y, Ishihara S, Amano K, Hirakawa K, Adachi K, Fukuda R, et al. An assessment of local curability of endoscopic surgery in early gastric cancer without satisfaction of current therapeutic indications. *Endoscopy* 1998;30:548-52.
10. Ono H, Kondo H, Gotoda T, Shirao K, Yamaguchi H, Saito D, et al. Endoscopic mucosal resection for treatment of early gastric cancer. *Gut* 2001;48:225-9.
11. Ono H, Gotoda T, Yamaguchi H, Kozu T, Fujii T, Kondo H, et al. A new method of EMR using an insulation-tipped diathermic knife [in Japanese with English abstract]. *Shoukaki Naishikyoku* 1999;11:675-81.