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• *RAPID COMMUNICATION* •

Risk factors for bleeding after endoscopic mucosal resection

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Abstract

AIM: To clarify the risk factors for bleeding after endoscopic mucosal resection (EMR).

METHODS: A total of 297 consecutive patients who underwent EMR were enrolled. Some of the patients had multiple lesions. Bleeding requiring endoscopic treatment was defined as bleeding after EMR. Odds ratios (OR) with 95% confidence intervals (CI), calculated by logistic regression with multivariate adjustments for covariates, were the measures of association.

RESULTS: Of the 297 patients, 57 (19.2%) patients with bleeding after EMR were confirmed. With multivariate adjustment, the cutting method of EMR, diameter, and endoscopic pattern of the tumor were associated with the risk of bleeding after EMR. The multivariate-adjusted OR for bleeding after EMR using endoscopic aspiration mucosectomy was 3.07 (95%CI, 1.59-5.92) compared with strip biopsy. The multiple-adjusted OR for bleeding after EMR for the highest quartile (16-50 mm) of tumor diameter was 5.63 (95%CI, 1.84-17.23) compared with that for the lowest (4-7 mm). The multiple-adjusted OR for bleeding after EMR for depressed type of tumor was 4.21 (95%CI, 1.75-10.10) compared with elevated type.

CONCLUSION: It is important to take tumor characteristics (tumor size and endoscopic pattern) and cutting method of EMR into consideration in predicting bleeding after EMR.

Key words: Endoscopic mucosal resection; Bleeding; Tumor characteristics; Cutting method

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INTRODUCTION

Endoscopic mucosal resection (EMR) of early gastric cancers has been widely accepted as a standard procedure because of its low degree of invasiveness and the excellent quality of life in patients[1-3]. Bleeding is one of the major complications of EMR for gastric lesions. The reported bleeding rate after EMR for early gastric cancers is between 1.4% and 20%[4-8]. As indications for EMR expands, more complications such as bleeding may occur with it. It is reported that patients who required blood transfusion after EMR due to severe bleeding account for 4-14% of all patients undergoing EMR[7,13]. Several factors related to bleeding after EMR, such as tumor diameter, have been reported[9]. Our aim is to clarify the risk factors for bleeding after EMR in 297 patients with gastric lesions.

MATERIALS AND METHODS

Study population

A total of 297 consecutive patients who underwent EMR between April 1991 and December 1997 in the Department of Gastroenterology of Osaka City University Medical School were enrolled. Inclusion criteria were all gastric lesions confined to the lamina propria. The depth of tumor invasion was determined by endoscopic ultrasound. There was no bleeding tendency in any of the studied patient, and no patients used drugs such as anticoagulants.

Methods and measurements

The gastric lesions were removed by strip biopsy or endoscopic aspiration mucosectomy. We defined early gastric cancer using the Japanese Classification of Gastric Carcinoma[9,10], and we have defined the absolute indication

for endoscopic treatment as follows: elevated type mucosal cancer less than 2 cm or depressed type mucosal cancer without ulceration less than 1 cm in size. We have also carried out endoscopic treatment in cases extending beyond these criteria as a relative indication, when we could not perform surgery due to patient's refusal or due to significant heart, lung or kidney failure. Strip biopsy was performed with a two-channel scope (GIF2T-200; Olympus Optical Co., Tokyo, Japan), as described by Tanabe *et al*[11]. Physiologic saline was injected locally to elevate the lesion. Endoscopic aspiration mucosectomy was performed as described by Torii[10]. A snare was introduced through a Teflon tube and tightened around the outer circumference of a transparent plastic cylinder cap (Olympus Optical Co., Tokyo, Japan). The Teflon tube, used as a snare introducer, was taped along the external axis of the endoscope. The snare was tightened by manipulating the handle, just as in polypectomy, and was fixed by taping it to the endoscope so that the snare loop remained at the tip of the cylinder cap. Physiologic saline was injected via an injection needle at the lesion to elevate the lesion. The snare was pushed over the tumor, while the lesion was aspirated along with the surrounding normal mucosa, and resection was performed by electrocauterization. A transparent cap was attached to the tip of an endoscope (GIFQ-200, GIFQ-230, GIFXQ-200, GIFXQ-230; Olympus Optical Co., Tokyo, Japan). The outer diameter of the transparent cap was 14.8 mm (MH-589) or 12.6 mm (MH-587).

Patients with a gastric lesion that required endoscopic treatment for bleeding after EMR were considered to have bleeding after EMR. We examined the patients with bleeding immediately after EMR, because they were treated with anti-ulcer drugs after EMR. Some of the patients had multiple lesions in our study in which the largest lesion per patient was selected as a representative lesion. Furthermore, when a patient had multiple tumors with the same largest diameter, we excluded the patient from analysis. We analyzed the data according to this rule.

The location of the lesion, tumor diameter, endoscopic pattern, histological findings for the tumor and cutting method were examined for their relationship to bleeding after EMR. After EMR, the removed mucosa was semifixed in formalin, and the lesion diameter was measured with a stereoscopic microscope (SZH-ILLB, Olympus Optical Co. Ltd., Tokyo, Japan). Based on the location, gastric lesions of the stomach was classified into an antrum group including the antrum and angle of the stomach, and a corpus group including the lower, middle, and upper body of the stomach. There were 158 lesions in the antrum group and 139 in the corpus group. By endoscopic pattern, lesions were classified into two types: elevated type and depressed type. There were 253 lesions of elevated type and 44 of depressed type. Histological examination revealed 139 early gastric cancers and 158 gastric adenomas[8]. We removed 177 lesions by the strip biopsy method and 144 lesions by endoscopic aspiration mucosectomy. Informed consent for EMR was obtained from all the patients.

Table 1 Baseline characteristics of study patients

	No bleeding after EMR (n = 240)	Bleeding after EMR (n = 57)	P
Age (yr)	65.3±9.3	66.0±8.4	0.582
Sex (M:F)	170:70	41:16:00	0.998
Tumor factors			
Location			
Antrum group	135 (85.4%)	23 (14.6%)	0.044
Corpus group	105 (75.5%)	34 (24.5%)	
Tumor diameter (mm)	12.4±6.7	13.9±7.1	0.152
Endoscopic pattern of lesion			
Elevated type	211 (83.4%)	42 (16.6%)	0.012
Depressed type	29 (65.9%)	15 (34.1%)	
Histological type			
Borderline adenoma	115 (82.7%)	24 (17.3%)	0.52
Cancer	125 (79.1%)	33 (20.9%)	
Cutting method			
Strip biopsy	156 (88.1%)	21 (11.9%)	0.001
Endoscopic aspiration mucosectomy	84 (70.0%)	36 (30.0%)	

Values are mean±SE or no. of gastric lesions.

Statistical analysis

Values were expressed as mean±SD. Categorical variables were compared using the χ^2 test. Differences in mean values between the two groups were compared using the unpaired t test. $P<0.05$ were considered significant. Multiple logistic regression analysis was used to evaluate the simultaneous effects of age, location of lesion, diameter, endoscopic pattern, histology of the tumor and the cutting method of EMR. Linear trends in risk associated with the tumor diameter were evaluated by indicators for each categorical level of tumor diameter using the median value for each category. The 95%CI for each odds ratio (OR) was calculated, and all P values are two-tailed. Statistical analyses were made using the SPSS 10.0 software package.

RESULTS

Of the 297 patients, 57 patients (19.2%) were confirmed to have bleeding after EMR. Baseline characteristics of the patients are summarized in Table 1. There was no significant difference in age and gender of patients, tumor diameter or histological type of tumor between the groups. The bleeding incidence after EMR in the corpus group was significantly higher than that in the antrum group (P = 0.038). The bleeding rate for depressed type lesions was significantly higher than that for elevated type lesions (P = 0.012). The bleeding rate with endoscopic aspiration mucosectomy was much higher than that with strip biopsy ($P<0.001$).

Of the 57 patients with bleeding, 18 (31.6%) patients had spurting bleeding (12 patients underwent EMR by endoscopic aspiration mucosectomy, and 6 underwent EMR by strip biopsy). Of these 57 patients, 39 (68.4%) had oozing bleeding (28 patients underwent EMR by endoscopic aspiration mucosectomy, and 11 underwent EMR by strip biopsy). All bleeding, except in one case, was controlled by endoscopic treatment with endoscopic clipping (HX5LR-1, Olympus, Japan), ethanol injection,

Table 2 Odds ratio of bleeding after endoscopic mucosal resection

	n	Cases	%	Crude-OR (95%CI)	Multiple-adjusted OR[1] (95% CI)	Multiple-adjusted OR[2] (95% CI)
Age (each additional year of age)	297	57	19.2	1.01 (0.98-1.05)	1.00 (0.97-1.04)	1.01 (0.97-1.04)
Tumor factors						
Location of gastric lesions						
Antrum group	158	23	14.6	1	1	1
Corpus group	139	34	24.5	2.24 (1.20-4.18)	2.24 (1.20-4.18)	1.69 (0.88-3.26)
Tumor diameter						
Quartile 1 (4-7)	58	5	8.6	1	1	1
Quartile 2 (8-11)	89	18	20.2	3.15 (1.06-9.38)	3.15 (1.06-9.38)	3.01 (0.99-9.07)
Quartile 3 (12-15)	76	13	17.1	2.53 (0.81-7.87)	2.53 (0.81-7.87)	2.90 (0.91-9.20)
Quartile 4 (16-50)	74	21	28.4	5.35 (1.78-16.10)	5.35 (1.78-16.10)	5.63 (1.84-17.23)
P for trend				0.048	0.022	0.022
Endoscopic pattern of lesion						
Elevated type	253	42	16.6	1	1	1
Depressed type	44	15	34.1	2.60 (1.28-5.26)	3.95 (1.69-9.24)	4.21 (1.75-10.10)
Histological type						
Adenoma	139	24	17.3	1	1	1
Cancer	158	33	20.9	1.27 (0.71-2.27)	0.67 (0.33-1.35)	0.56 (0.27-1.16)
Cutting method						
Strip biopsy	177	17	9.6	1		1
Endoscopic aspiration mucosectomy	120	40	33.3	3.18 (1.75-5.80)		3.07(1.59-5.92)

[1]Adjusted for age, tumor factors, location of gastric lesions, tumor diameter, endoscopic pattern of lesion, histological type. AT indicates antrum of stomach; [2]Adjusted for age, tumor factors, location of gastric lesions, tumor diameter, endoscopic pattern of lesion, histological type, and cutting method.

and injection of hypertonic saline-epinephrine solution. No patient required blood transfusion in our study, only one patient underwent open emergency surgery because of severe bleeding after EMR.

Multivariate analysis of bleeding risk after EMR

The multivariate analysis of bleeding after EMR is summarized in Table 2. Cutting method of EMR was the strongest factor identified in this analysis. Location of gastric lesion, tumor diameter, and endoscopic pattern of the lesion were associated with an increased risk of bleeding after EMR, when the multivariate analysis was adjusted for age, location of gastric lesions, tumor diameter, endoscopic pattern of lesion and histological type. However, when cutting method of EMR was added to these factors in the multivariate analysis, location of the gastric lesion was no longer a significant factor. The multiple-adjusted OR excluding the factor of the cutting method for bleeding after EMR in the corpus group was 2.24 (95%CI, 1.20-4.18) compared with that in the antrum group. However, the multiple-adjusted OR including the factor of cutting method for bleeding after EMR in the corpus group was 1.69 (95%CI, 0.88-3.26) compared with that in the antrum group.

Tumor diameter and endoscopic pattern of the lesion were not significant factors in the multiple-adjusted analysis, either including or excluding the factor of cutting method. To examine in detail the risk of tumor diameter, tumor diameter was divided into four categories. The multiple-adjusted OR including the factor of cutting method for the highest quartile of diameter was 5.63 (95%CI, 1.84-17.23) compared with that for the lowest.

Concerning endoscopic pattern of lesions, the multiple-adjusted OR for depressed type lesions with the inclusion of the factor of cutting method was 4.21 (95%CI, 1.75-10.10) compared with that for elevated type lesions. The multiple-adjusted OR for bleeding after EMR with endoscopic aspiration mucosectomy was 3.07 (95%CI, 1.59-5.92) compared with that for strip biopsy.

On crude analysis, the histology of the lesion was also associated with the risk of bleeding after EMR, but in the multiple-adjusted analyses this association was not significant.

DISCUSSION

EMR is an established treatment for early-stage gastric cancers, and is an alternative to surgery for patients with superficial neoplastic lesions of the digestive tract. EMR can achieve a complete resection in a majority of patients, but is associated with a higher risk of bleeding than standard polypectomy[4-7,13,14]. Bleeding incidence, however, appears to vary according to how bleeding is defined. Bleeding during EMR of colorectal polyp is common, occurring in 24% of polypectomy of large colorectal polyps[15]. Morales *et al*[15] defined procedural bleeding as a complication. Various forms of endoscopic treatment, such as multipolar electrocoagulation, use of heat probe, and injection therapy, are usually highly effective in stopping acute upper gastrointestinal ulcer bleeding[16-18]. Similarly, bleeding during the performance of EMR can almost always be controlled by the injection of saline epinephrine solution, thermal coagulation, or endoscopic clipping[25]. Endoscopic clipping is believed to be the safest therapeutic modality for controlling spurting bleeding after EMR[19,20,23]. However, it is reported that patients who required blood transfusion after EMR due to large bleeding accounted for 4-14% of patients undergoing EMR[7,13].

We came across one patient who underwent open emergency surgery because of severe bleeding after EMR.

Most bleeding occurs during the procedure, although delayed bleeding (up to 3 d in 10% of patients) has been reported[15]. In our study, patients with a gastric lesion that required endoscopic treatment for bleeding after EMR were considered to be cases to have bleeding after EMR.

The association of various factors with bleeding rates, such as tumor diameter[13], diameter of the removed mucosa, cutting method[6,12,13,21], location of gastric lesions, endoscopic pattern of lesions[13], and histological type of gastric tumor has been reported[6]. Those studies examined not only the risk of bleeding but also the rate of bleeding.

We found that tumor diameter, endoscopic pattern of lesions, and cutting method were associated with the increased risk of bleeding after EMR. These associations existed even on multivariate analysis.

It has been reported that larger diameter tumors bled readily after EMR[13]. We evaluated linear trends in risks of tumor diameter by indicators for each categorical level, and found that the findings were consistent with our results from the previous reports. We used tumor diameter determined by postfixation measurement as a predictor of post-EMR bleeding, because formalin fixation did not cause shrinkage of the specimens[22-23].

No significant relationship was found between bleeding incidence and the cutting diameter[12], and large cutting diameter was easy to bleed, because bleeding incidence may depend on the size of the cutting diameter[24]. We did not evaluate the diameter of the removed mucosa because this factor could not be measured before EMR was undertaken, and therefore could not be a predictor of bleeding.

Submucosal injection is an important part of the EMR procedure. Injection of fluid into the submucosa beneath a gastric lesion increases the distance between the base of the polyp and the deeper tissues of the gastric wall. It has been reported that a large submucosal cushion of saline solution increases the safety of polypectomy by preventing thermal injury to these deeper tissues[26,27]. Therefore, submucosal injection may influence bleeding after EMR. However, effects of the volume of physiologic saline solution injected were not investigated in our study, because the administration volume of physiologic saline solution was not routinely recorded. The endoscopic pattern of the lesion influences the risk of bleeding after EMR has not been reported. Depressed type lesion was a risk factor for bleeding after EMR in our study. However, the volume of submucosal injection used may have affected this result.

There is one report that bleeding incidence is higher with strip biopsy than with endoscopic aspiration mucosectomy, a finding inconsistent with our results[21]. It was reported that the size of resected specimens was significantly larger with endoscopic aspiration mucosectomy than with strip biopsy[11]. We did not evaluate the diameter of the removed mucosa in our study, though it might influence the bleeding rate associated with the cutting method.

Blood vessel diameter in the antral region of the stomach is smaller than that in the gastric corpus, and the number of blood vessels in the antral region is low[27]. In our study, no significant relationship was found between the locations of the lesion and cutting method in multivariate analysis. However, the bleeding incidence in the corpus group [24.5% (34/139)] was higher than that in the antrum group [14.6% (23/158)]. Therefore, if the sample size of our study was enlarged, a significant difference might be found.

Of the 297 patients, 64 (21.5%) patients underwent EMR by piecemeal resection, with a bleeding incidence of 15.6% (10/64). A total of 233 (78.5%) patients underwent EMR by en-bloc resection, with a bleeding incidence of 20.2% (47/233). There was no significant relationship between *en-bloc* resection or piecemeal resections and bleeding incidence after EMR.

In our study, ten endoscopists performed EMR for patients with bleeding after EMR. Categorical variables, such as location of the lesion, tumor diameter (four categories), endoscopic pattern, histology of the tumor and cutting method were compared among the 10 endoscopists using the χ^2 test. There was no significant difference among the endoscopists in the location of lesion ($P = 0.618$), tumor diameter ($P = 0.182$), endoscopic pattern ($P = 0.374$), histology of the tumor ($P = 0.395$) or cutting method ($P = 0.138$). Therefore, the particular endoscopist performing the procedure did not influence the risk of bleeding.

Conio *et al* divided the definition of "bleeding after EMR" into three categories, i.e., intraprocedure (occurring during EMR), early (within 24 h), and delayed (≧24 h). In our study, "bleeding after EMR" was defined as intraprocedure.

In conclusion, our study indicated that tumor diameter, endoscopic pattern of lesions, and cutting method are risk factors for bleeding after EMR. It is important to consider these three factors in predicting bleeding after EMR.

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