Original article

Indications for gastrectomy after incomplete EMR for early gastric cancer

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Abstract

Background. Although the number of patients with early gastric cancer (EGC) treated by endoscopic mucosal resection (EMR) has increased, the appropriate strategy for treating those with incomplete resection has not been established.

Methods. This study analyzed 726 cases of EGC in patients treated by EMR between 1991 and 2000, in order to clarify the en-bloc and complete resection rates. We classified patients with incomplete resection into four groups according to the estimated risk of residual cancer or lymph node (LN) metastasis, determined from pathological findings of EMR specimens. We then analyzed 45 patients with EGC treated surgically after incomplete EMR, with the aim of eliciting the risk of residual cancer and LN metastasis.

Results. Of the 726 patients, 529 (72.9%) had an en-bloc resection, while 378 (52.1%) had a complete resection. Three hundred and nine patients were found to have mucosal cancer and lateral cut-end-positive status with no LN metastasis (group A). In this group, 18 patients (5.8%) had residual cancer, with the lesions in the majority of patients being limited to the mucosal layer. Group B consisted of 14 patients with differentiated and submucosal (sm1) depth cancers, with 1 patient having residual cancer and 2 patients having LN metastasis. Fifteen patients were classified as group C, with sm2 or greater and vertical cut end-negative status, with 2 showing residual cancer and 1 showing LN metastasis. Group D included 10 patients with vertical cut end-positive status. Four of these patients had residual cancer while 1 had LN metastasis.

Conclusion. We recommend that patients in group A should have close follow-up or endoscopic treatment, while those in groups B, C, or D should be treated by gastrectomy associated with LN dissection.

Key words Gastric cancer · Endoscopic mucosal resection · Residual cancer · Lymph node metastasis

Introduction

The number of patients with early gastric cancer (EGC) treated by endoscopic mucosal resection (EMR) has increased [1,2]. This trend reflects the increase in EGC cases identified by improvements in both diagnostic devices and EMR techniques [3–10]. Many patients suffering from EGC have received benefits from these advances and have avoided laparotomy and maintained a better quality of life (QOL) [1,11,12]. However, of the patients treated by EMR there are occasionally patients that have incomplete resections [1,2,13]. While such patients are treated empirically, by either gastrectomy, additional endoscopic treatment, or careful follow up [1,4,14], there is no defined strategy to treat these patients that takes into account the real risks. In these circumstances, inappropriate additional treatments may reduce the patients' QOL or lead to adverse outcomes. Since 1991, we have carried out a prospective study to investigate the treatment of patients with incomplete EMR according to estimated risks. After the risk of tumor recurrence or lymph node metastasis was considered, either close follow-up or gastrectomy associated with lymph node dissection was performed. The present study aimed to clarify the incidence of en-bloc and complete resections and to evaluate the adequacy of our therapeutic strategy by determining the risk of residual cancer or lymph node metastasis.

Patients and methods

The subjects of the study were 726 patients who underwent EMR for primary gastric cancer between January 1991 and December 2000. Surgically treated patients with specific conditions, such as metachronous multiple carcinoma after EMR, gastric wall perforation during the procedure or uncontrollable bleeding, or those who received palliative EMR for submucosal

Table 1. Criteria for complete resection and classification of incomplete resection

Patients (726) treated by EMR (1991–2000)

- [Complete resection: mucosal cancer and no cancer exposure to any cut end
 Incomplete resection: not a complete resection, classified according to the following categories
- [Group A, mucosal cancer and lateral cut end-positive
 Group B, differentiated and sm1 depth
 Group C, sm2 or more and vertical cut end-negative
 Group D, vertical cut end-positive
-

gastric cancer with poor surgical risk were not included in the study.

We reviewed the clinical records of the selected patients to determine the en-bloc and complete resection rates and then classified the patients with incomplete resection into groups according to their estimated risk, as described below. We then investigated their clinical courses and calculated the risk of residual cancer or lymph node metastasis for each group by the evaluation of surgical specimens.

Indications of EMR for gastric cancer

Since late 1988 we have regarded the following features as indicating the need for EMR, and accordingly applied these criteria prospectively.

- (1) Histologically differentiated-type carcinoma (pap, tub1, or tub2) limited to the mucosal layer, without ulceration or ulcer scars and with a spread of no more than 30 mm.
- (2) Undifferentiated-type carcinoma remaining in the intramucosal layer without ulceration or ulcer scars and limited to 5 mm in size. In this series, we applied this indication prospectively, regardless of the lesion's gross appearance, such as elevated, flat, or depressed.

Methodology of EMR and criteria of complete resection

In the early period of the decade 1991–2000, we mainly used the strip biopsy method [3]. However, in the latter period of the decade, with the objective of obtaining better hemostasis, we used a hypertonic saline-epinephrine solution (HSE solution) instead of the physiological saline solution used in the original strip biopsy [5]. In addition, we applied other methods, such as cap-fitted aspiration mucosal resection [6,7], determined by technical considerations of the size and position of the lesion [12,15] and the equipment and expertise of the operators. For relatively large lesions (≤ 30 mm) we occasionally used designed multi-fragment resection [13].

Each resected specimen was extended immediately and fixed with pins on a cork board to prevent rolling of the edges, followed by morphological observation and two-dimensional measurements. In the patients treated with the multi-fragment method, the specimens were immediately reconstructed by the operator.

Patients who were considered to have had a curative resection had no cancer exposure to any cut end (Table 1) and the line between normal tissue and the portion denatured by burning or mechanical effect remained in the mucosal layer, regardless of whether en-bloc resection or multi-fragment resection had been performed.

Classification of patients with incomplete resection, and therapeutic strategy

For the investigation, we classified the patients with incomplete EMR into four groups, using the system outlined in Table 1. The groups were: group A, tumors limited to the mucosal layer and exposed to the lateral cut end, or tumors with a lateral cut end that could not be evaluated due to burning or mechanical damage caused by the EMR, but in which any residual cancer present would have been limited to the mucosal layer. Group B, tumors with a differentiated histological structure that had invaded within 500 μ m of the surface of the submucosal layer (sm1), and tumors that may have been exposed to the lateral cut margin in the mucosal layer but not to the vertical cut margin. Patients were included in Group C if lymphatic-vascular involvement in the submucosal layer was observed [16]. Group C, tumors with massive infiltration of the submucosal layer (sm2 or more), but not exposed to the vertical cut end. Patients with undifferentiated-type tumors and those limited to the surface of the submucosal layer were included in this group. Group D, tumors exposed to the vertical cut end, with infiltration of sm2 or more. Both groups C and D included patients with positive lateral cut ends and patients with lymphatic or vascular involvement in the submucosal layer.

In the recent decade of the study, we applied a prospective strategy for patients with incomplete EMR, using the following system. For intramucosal cancers

Table 2. Incidence of complete and incomplete resection, and details of patients with incomplete resection

Patients (726) treated by EMR (1991–2000)		
→	Complete resection	378 Patients (52.1%)
	Incomplete resection	348 Patients (47.9%)
→	Group A	309 Patients (88.8%)
	Follow-up	288 Patients → No recurrence
	Surgery	21 Patients (6.8%)
	Residual cancer	18 Patients (5.8%)*
→	Group B	14 Patients (4.0%)
	Follow-up	11 Patients → No recurrence
	Surgery	3 Patients (21.4%)
	Residual cancer	1 Patient (7.1%)*
→	Group C	15 Patients (4.3%)
	Follow-up	4 Patients → No recurrence
	Surgery	11 Patients (73.3%)
	Residual cancer	2 Patients (13.3%)*
→	Group D	10 Patients (2.9%)
	Follow-up	None
	Surgery	10 Patients (100%)
	Residual cancer	4 Patients (40%)*
	LN metastasis	1 Patient (10%)*

* $P < 0.001$ vs group A

with lateral residue revealed by histological examination, if the amount of cancer was interpreted as minute, we followed the patient conservatively or carried out additional endoscopic treatment. However, if the case proved impossible to treat endoscopically or if the extent of the tumor was larger than that at initial EMR, we recommended surgical resection associated with lymph node dissection. In patients in whom the cancer had invaded the surface of the submucosal layer we explained the low risk of lymph node metastasis to the patients and requested them to choose between close follow-up or surgery. Patients with massive infiltration of the tumor to the submucosal layer, regardless of vertical cut-end status or lymphatic-vessel involvement, were strongly recommended to have surgical resection with level 2 lymph node dissection.

All technical terms used in this report are in accordance with the *Japanese classification of gastric carcinoma*, 2nd English edition [17].

Statistical analysis

The Mann-Whitney *U*-test was used for statistical analysis of the data, with *P* values of less than 0.05 being considered significant.

Results

Incidence of incomplete EMR (Table 2)

Of the 726 patients, 529 (72.9%) were treated by en-bloc resection, with 378 (52.1%), including those

treated by multi-fragment resection, fulfilling the criteria for curative (complete) resection. None of these patients had a recurrence of cancer and none had a cancer-related death. Of the 348 patients with incomplete resection, 309 (88.8%) were classified as group A, 14 (4.0%) as group B, 15 (4.3%) as group C, and 10 (2.9%) as group D. We carefully followed 303 of these patients with incomplete resection, with the remaining 45 receiving surgery. All of the patients with incomplete resection were cured.

Evaluation of patients with additional surgery

Of the 348 patients with incomplete EMR, 45 patients (12.9%) received surgical treatment, representing 6.2% of all the subjects. The surgical conversion rate showed the following incremental increases in the groups classified according to our criteria. Additional surgery was performed in 21 patients (6.8%) classified as group A, 3 (21.4%) classified as group B, 11 (73.3%) classified as group C, and 10 (100%) classified as group D.

Among the 21 patients in group A, 3 (14.3%) did not show residual cancer, whereas 18 (85.7%) had microscopic evidence of residual cancer in the stomach. These 18 patients with residual cancer represented 5.8% of the 309 patients in Group A. Only 2 patients in group A (0.6%) were found to have submucosal residual cancer. Regarding the manner of resection, 17 patients (81.0%) were treated by en-bloc resection, while 4 (19.0%) were treated by multi-fragment resection. Sixteen patients with en-bloc resection and 2 with multi-fragment resection were shown to be residual

cancer-positive. No patient in group A had lymph node metastasis.

Three patients in group B (21.4%) received surgical treatment, with one showing residual cancer in the stomach, without lymph node metastasis. The other two patients, representing 14.3% of group B, had lymph node metastasis, despite having residual cancer-negative status in the stomach.

Fifteen of the 348 patients with incomplete EMR were classified as group C. We explained the necessity for surgery to the patients, although 4 individuals refused this option. None of these 4 patients had a recurrence of cancer or a cancer-related death. Of the 11 patients who received surgery, 9 had no residual cancer around the EMR scar, while 2 had lesions in the stomach. In one patient, the cancer was restricted to the mucosal layer, whereas in the other patient it had invaded deeply into the submucosal layer. These 2 patients did not have lymph node metastases. Regional lymph node metastases were found in 1 patient, representing 6.7% of group C.

All ten patients in group D received surgery, with 6 (60.0%) being free from residual cancer; one patient had residual cancer in the mucosal layer, while three had lesions in the submucosal layer. This group had more macroscopically depressed-type lesions compared to group C (six elevated type / five depressed type in group C; three elevated type / seven depressed type in group D). Lymph node metastases were revealed in one patient (10.0%). Statistical analysis demonstrated that there was a significantly higher incidence of residual cancer and lymph node metastasis in groups B, C, and D compared with group A.

Details of node-positive patients (Table 3)

Four patients had lymph node metastases, representing 1.1% of those with incomplete EMR and 8.9% of those with additional surgery. Two patients were classified as group B, one as group C, and one as group D.

One of the patients in group B had lateral cut end-positive status and lymphatic involvement limited to the muscularis mucosa. Follow-up abdominal computed tomography (CT), taken 2 years after the EMR revealed lymph node swelling in the infra-pyloric region and, therefore, further surgery was performed. Level 1 lymph node metastasis was revealed, although residual cancer in the stomach was not found.

The other patient in group B had lateral cut end-positive status and a relatively wide extent of submucosal invasion. Although the submucosal part of the tumor consisted mostly of well differentiated tubular adenocarcinoma (tub1), histological heterogeneity was also seen, with a poorly differentiated component being observed. Surgery was carried out, and level

Table 3. Details of four patients with LN metastasis

	Group	Gross type	Size (mm)	Histological type	Depth of invasion at EMR	Lateral cut end	Lymphatic involvement	En bloc or multi-fragment	Site of LN metastasis	Depth of invasion behind the stomach
Case 1	B	I+IIc	15	tub1	sm1	(+)	(+) ^a	En bloc	No. 6 (3 LNs)	No cancer
Case 2	B	IIc	12	tub1	sm1	(+)	(-)	Multi-fragment	Nos. 3, 11p (3 LNs)	No cancer
Case 3	C	IIa	14	tub2	sm2	(-)	(+)	En bloc	No. 4d (3 LNs)	No cancer
Case 4	D	I	30	tub2	sm2 or more	(-)	(-)	Multi-fragment	No. 2 (2 LNs)	sm2

Group B, differentiated and sm1 depth; group C, sm2 or more and vertical cut end-negative; group D, vertical cut end-positive

^aLimited to the muscularis mucosa

2 lymph node metastasis was revealed, although no residual cancer was found in the stomach.

One patient, in group C, with sm2 invasion and lymphatic involvement at EMR, showed level 1 lymph node metastasis, although no residual cancer was found in the stomach.

In group D, one patient had level 1 lymph node metastasis associated with residual cancer in the stomach that reached a depth of sm2 or more.

Discussion

The use of endoscopic mucosal resection (EMR) in selected patients with early gastric cancer (EGC) is an accepted surgical approach. Despite many patients with node-negative EGC having a better quality of life (QOL) after EMR, there remain some unsolved problems associated with this treatment.

The Japanese Gastric Cancer Association [18] has published guidelines for the treatment of gastric cancer that include indications for EMR in patients, considered to have a very low risk of lymph node metastasis. The present study started prior to the publication of these guidelines, and in accordance with the accumulation and analysis of our own institution's data, used a wider range of indications than that contained in the guidelines. These included large differentiated-type lesions and small undifferentiated-type lesions.

With regard to therapeutic strategy after an incomplete EMR, Korenaga et al. [12] emphasized that a gastrectomy should be performed in patients in whom the cancer had invaded the submucosal layer, whereas noninvasive treatment should be used in patients in whom the cancer had extended to the mucosa around the margin. However, Gotoda et al. [2] demonstrated that there was no risk of lymph node metastasis in patients who fulfilled the following conditions; differentiated adenocarcinoma, no lymphatic-vascular invasion, tumors less than 3 cm in size, and submucosal invasive cancer less than 500 μ m in depth. Ono et al. [1] reported the risk of recurrence even following complete resection in patients who had had multiple-fragment resection. A strategy for confinement has not been established and requires further discussion.

At the start of this study we determined the appropriate treatment after incomplete EMR for gastric cancer by employing a strategy based on the following estimated risks. We assumed classification to group A when the residual tumor, if present, was limited to the mucosal layer. The causes responsible for this insufficient removal of the cancer were either technical difficulty or inaccurate diagnosis regarding the extent of the tumor, but correct assessment of the depth of tumor invasion. We considered that it was possible to treat this group

using endoscopy. Our study revealed a low rate of surgical conversion in group A (6.8%; 21/309) and a low rate of residual cancer (5.8%; 18/309). With the exception of 2 patients (0.65%; 2/309) who had submucosal invasion, 16 patients were found to have residual cancer in the mucosal layer. Multi-fragment resection was observed in 4 of 21 (19.0%) surgically treated patients in group A. This proportion was lower than that found in the 726 patients as a whole (27.1%). Moreover, residual cancer positivity was more common in the patients with en-bloc resection (94.1%), with multi-fragment resection appearing not to increase the risk of residual cancer. We consider that our results indicate that conventional gastrectomy associated with D2 lymph node dissection may be too invasive a procedure for this group (group A). According to the Japanese Gastric Cancer Association (JGCA) gastric cancer treatment guidelines, for patients with cancers of T1 (m or sm) and N0, apart from EMR, modified gastrectomies are recommended, regardless of the microscopic differentiation of the cancer. For these procedures, vagus preservation, pylorus preservation, or laparoscopic approaches are permitted as options [19]. However, in patients who would be difficult to treat endoscopically, application of these surgical options would be favorable.

We assumed that patients diagnosed as having differentiated tubular adenocarcinoma that had infiltrated the surface of the submucosal layer (sm1) would be classified as group B. In 1985, Korenaga et al. [20] demonstrated the risk of lymph node metastasis in association with lesions invading the superficial submucosal layer. While not disregarding this risk, even without ductal involvement, we were not able to determine the real incidence of such lymph node metastasis, due to the small number of patients. Accordingly, we selected patients either for additional surgery or for close follow-up. Two node-positive patients (14.3%) were identified in group B, and they exhibited specific findings, such as histological heterogeneity [21] or lymphatic involvement in the muscularis mucosa. These two cases indicated that even small sm1 cancers are not free of the risk of lymph node metastasis. Further data collection and analysis are necessary to better understand the process of this metastasis.

Patients were assigned to group C if the primary cancer showed massive invasion of the submucosal layer but had been removed from the aspect of the vertical cut end. In accordance with the high incidence of lymph node metastasis in submucosal gastric cancers, surgery was considered mandatory in these patients. Our series revealed a 9.1% prevalence rate of lymph node positivity. In group C, if the depth of the primary lesion was confirmed by initial EMR, and if the lesion fulfilled the criteria for stage IA, a modified gastrectomy was recom-

mended, in accordance with the JGCA gastric cancer treatment guidelines.

Group D included patients with massive invasion of the primary cancer into the submucosal layer or deeper, associated with incomplete resection, as evidenced by residual cancer at the vertical cut end. In this group, residual cancer may have remained in the deep submucosal layer or below. As expected, the incidence of local residual cancer was greater and the depth of the lesions deeper than those in group C. Surgery was mandatory in this group, with a gastrectomy associated with lymph node dissection being required.

Retrospective assessment of the adequacy of our classification system and strategies showed that group A had no risk of lymph node metastasis and a low rate of residual mucosal cancer. This finding confirmed the adequacy of our strategy, if the application of modified surgical options was removed. Group B included lymph-node-positive patients. The number of these patients was too small to decide upon a confirmed strategy, with the accuracy of CT staging for lymph node metastasis in gastric cancer remaining controversial [22–24]. However, it appears to be difficult to diagnose lymph node recurrence precisely and early enough, even if close follow-up by CT is conducted. In these patients, additional surgery would be needed and further examination would be necessary. Groups C and D showed the expected risks, and supported our strategy of an absolute indication for surgery.

In this series, we elucidated the risk of localized residual cancer and lymph node metastasis for each of four types of incomplete EMR. We consider that an appropriate strategy should be applied for patients with incomplete EMR according to a system that incorporates categories of estimated risk. Such a system would minimize the reduction in QOL that results from unnecessary operations and inadequate follow-up. Moreover, the guarantee of a strategy for incomplete EMR would improve QOL in the majority of patients with EGC who undergo this procedure.

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