

Long term outcomes comparing between endoscopic mucosal resection and traditional gastrectomy for treatment of early gastric cancer

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Abstract

Aims The purpose of this study was to confirm whether the endoscopic mucosal resection for early gastric cancer replaced the traditional gastrectomy on the view point of long term patients' outcomes.

Methods Among consecutive series of 1298 patients with early gastric cancer (EGC), a total of 214 cases with EGC endoscopically resected from May 1989 and December 2001 were included in the study. Among them 26 patients (11.6%) underwent additional EMR followed by surgery, because of the residual cancer, and they received 17 distal gastrectomy (DG), 7 proximal gastrectomy (PG), and 2 total gastrectomy (TG). The rest 188 patients were received EMR only and were followed without gastrectomy. Eight hundred fifteen patients received DG, 135 PG, 107 TG, 11 wedge-resection of the stomach and 5 resection of the rest stomach between July 1975 and December 2001. Between July 1975 and April 1989, 369 patients received distal gastrectomy (DG), 30 proximal gastrectomy (PG), 52 total gastrectomy (TG), 2 wedge-resection of the stomach and 2 resection of the rest stomach.

Results Ten-year survival rates of patients underwent distal G, PG, TG, wedge-resection, resection of the rest stomach, and EMR were, 81.1%, 70.4%, 52.0%, 42.1%, 0%, and 49.2%, respectively. There were significant differences between DG and EMR (log rank test, $p < 0.0001$).

Among mucosal cancer patients 18/500(3.6%), 1/66(1.5%), 1/48(2.1%), and 1/183(0.5%) who received DG, PG, TG, and EMR were disease specific death in this analysis. Among submucosal cancer patients, 14/335(4.2%), 0/76(0%), 5/59(8.5%), and 1/15(6.7%) who received DG, PG, TG, and EMR were disease specific death.

Comparing to the patients between receiving EMR alone, and gastrectomy after EMR, and between indicated ERM patients by criteria of the Japanese Gastroenterology Endoscopy Society and no-indicated patients, the former was better outcome than the latter, and also showed to not be better than those with distal gastrectomy.

Conclusions The outcome of patients who received EMR were not better than those who received distal gastrectomy, however, it is important to treat with minute and small cancer patients such as early cancer by endoscopy on the view point of patients' QOL. From our results doctors who treat cancer patients by endoscopy, must guide the important of the restriction of diet in cancer patients, which is not correlate to cure cancer, but to patients' good QOL as well as persons without cancer.

Key words: early gastric cancer, endoscopic mucosal resection, traditional gastrectomy, histology

(Received March 5, 2005; Accepted May 30, 2005)

Introduction

The incidence of early-localized gastric cancers increased and that of advanced invasive cancers decreased in Japan during the past 20 years¹⁾. Moreover, large retrospective series and our data have demonstrated that early gastric cancers have a low risk of lymph node metastasis, and have good outcome after gastrectomy. Endoscopic treatment, that is, endoscopic mucosal resection (EMR) and laparoscopic surgery, has become increasingly popular in recent years as an alternative to surgical treatment with the hope of offering superior quality of life (QOL)

for the patient. We started to treat early gastric cancer patients by EMR from April 1989. In Japan, the substantial increase of early detection due to screening endoscopy has contributed to the introduction and development over the past decade of endoscopic mucosal resection (EMR) in the treatment of early gastric cancer. This patient's highly friendly treatment offering a very high quality of life (QOL) and associated with low morbidity has become very popular in Japan. EMR was developing to be used for diagnosis, and treat for gastric cancer²⁾.

Recent advances in technology, refinement of the technique and increased experience and skill of Japanese endoscopists have resulted in the establishment of EMR as the treatment of choice of early-stage cancer in Japan. Currently, the Japanese Gastric Cancer Association recommends EMR for small (< 2 cm) histologically dif-

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ferentiated mucosal cancers irrespective of macroscopic appearance. Many surgeons as well as endoscopic doctors would be convinced that EMR of gastric neoplasmas is a curative technique that avoids surgery and its potential complications, and also that by this treatment patients will have good outcomes. But, cost benefit of re-examination and long-term outcome data are lacking. Moreover, no reports are aware of the focus on the survival compared with the outcome of traditional gastrectomy in the period when EMR was not introduced.

In this study, we access to compare the outcomes of patients, who treated with EMR and those receiving gastrectomies for early gastric cancer.

Materials and Methods

A consecutive series of 1298 patients with early gastric cancer (EGC), who diagnosed as pathological early gastric cancer between July 1975 and December 2001, and whose tumors invaded to the mucosal and the submucosal layer without lymph node metastasis in the cases of the traditional gastrectomy, and whose tumors invaded to the mucosal and the submucosal layer without possible lymph node metastasis in the cases of EMR. They all diagnosed as EGC at the time of the preoperative endoscopy and upper gastroenterological examination. Among them a total of 214 cases with EGC endoscopically resected from May 1989 and December 2001 were included in the study. Among them 26 patients (11.6%) underwent additional EMR followed by surgery, because of the residual cancer, and they received 17 distal gastrectomy (DG), 7 proximal gastrectomy (PG), and 2 total gastrectomy (TG). The rest 188 patients were received EMR only and were followed without gastrectomy. Eight hundred fifteen patients received DG, 135 PG, 107 TG, 11 wedge-resection of the stomach and 5 resection of the rest stomach between July 1975 and December 2001. Between July 1975 and April 1989, 369 patients received distal gastrectomy (DG), 30 proximal gastrectomy (PG), 52 total gastrectomy (TG), 2 wedge-resection of the stomach and 2 resection of the rest stomach.

Our indication for EMR was only that tumors were small early cancers without possible lymphnode metastases and was able to remove cancers with EMR treatment. As a result, under the guideline of the indication criteria proposed by the Japanese Gastroenterology Endoscopy Society 36 cases were not indicated for EMR. Among the indicated (n=174) and not indicated cases (n=50), consequently, 12 and 14 received gastrectomy, respectively. Among EMR patients (n=198) 11 were followed having recurrent tumors at the time of study on December 2004.

All patients who underwent traditional gastrectomy received over D2 lymph node dissection. Surgical techniques were reported elsewhere. Patients' ages ranged from 24 to 88 years (median: 61 years), and 75.4% were

male. Final pathological diagnosis and classification of the patients with operation and EMR were carried out using the resected stomach and specimens of endoscopic mucosal resection according to the general rules for the gastric cancer study in surgery and pathology in Japan. Median follow-up-period was 4821, 3746, 5117, 3577, 3492, and 2064 days in the patients who underwent DG, PG, TG, wedge resection, resection of the rest stomach, and EMR, respectively.

Statistical analysis

Mean values were compared by Student's t-test. The chi-square test was used to compare the prevalence of characteristics. Results were considered significant when the P value was less than 0.05. Survival curves were calculated using the Kaplan-Meier product-limit estimate and differences in survival were assessed by the Log-rank. P values of less than 0.05 were considered to be significant. All statistical analyses were carried out using SPSS 12.0 software (SPSS Inc., Chicago, USA.).

Results

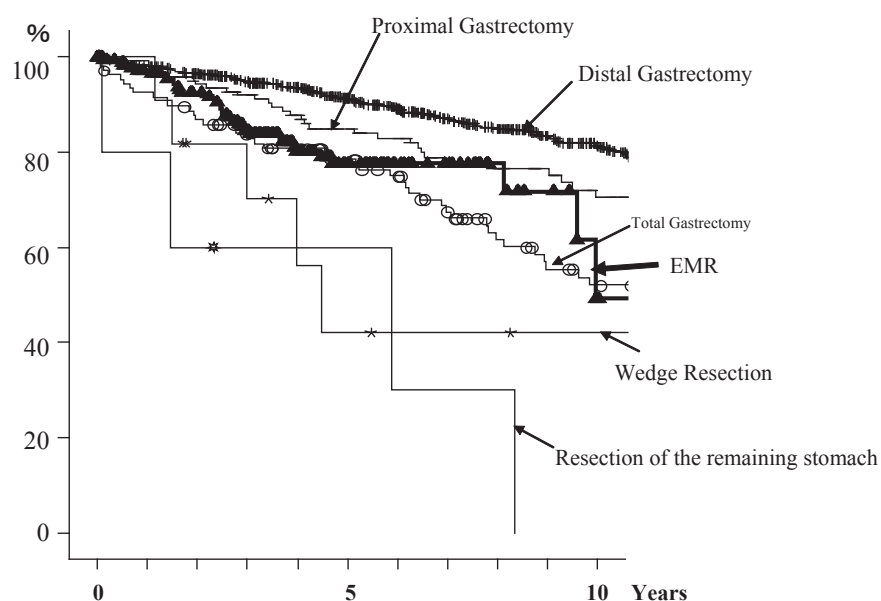
Patients' characteristic and the outcomes of the patients were showed in Table 1. Among mucosal cancer patients 18/500(3.6%), 1/66(1.5%), 1/48(2.1%), and 1/183(0.5%) who received DG, PG, TG, and EMR were disease specific death in this analysis. Among submucosal cancer patients 14/335(4.2%), 0/76(0%), 5/59(8.5%), and 1/15(6.7%) who received DG, PG, TG, and EMR were disease specific death.

Fig. 1 showed the survival curves of patients. Ten-year survival rates of patients underwent DG, PG, TG, wedge-resection, resection of the rest stomach, and EMR were, 81.1%, 70.4%, 52.0%, 42.1%, 0%, and 49.2%, respectively. There were significant differences between DG and PG, TG, wedge resection, resection of the rest stomach, and EMR (log rank test, $p=0.019$, $p<0.0001$, $p=0.0001$, $p<0.0001$, and $p<0.0001$, respectively.), and between PG and TG, wedge resection, and resection of the rest stomach (log rank test, $p=0.0092$, $p=0.0161$, and $p<0.0001$, respectively.), and between TG and resection of the rest stomach (log rank test, $p=0.0083$), and between EMR and resection of the rest stomach (log rank test, $p=0.0009$).

Fig. 2 showed the survival curves of the mucosal cancer patients during July 1975 to April 1989 and those during May 1989 to December 2001, who received DG, PG, TG, wedge-resection, resection of the rest stomach and EMR. Ten-year survival rates of patients receiving DG, PG, and TG during July 1975 to April 1989 were 84.4%, 71.4%, and 56.1%, respectively. There were significant differences between TG and DG (log rank test, $p=0.0048$). Five-year survival rates of patients receiving

Table 1 Patients' characteristic and the outcomes of the patients

	Distal gastrectomy	Proximal gastrectomy	Total gastrectomy	Wedge resection	Resection of the remaining stomach	EMR	Total
Total	n=835	n=142	n=107	n=11	n=5	n=198	n=1298
Median age(range)	59(24-88)	62(28-85)	63(26-84)	74(43-88)	71(62-77)	67(40-88)	61(24-88)
Gender							
F	221	37	19	3	0	39	319
M	614	105	88	8	5	159	979
Operation							
Aug. 1975-Oct. 1989	369	30	52	2	2	0	455
Nov. 1989-Dec. 2001	466	112	55	9	3	198	843
Depth of cancer							
Mucosa	500	66	48	6	3	183	806
Submucosa	335	76	59	5	2	15	492
Tumor size(mm)	25.3	23.7	34.6	18.4	13.7	12.7	25.8
Histology							
Diff.	526	93	70	9	3	192	893
Undiff.	305	47	34	2	2	5	395
Mixed	4	2	3	0	0	1	10
Location cancer							
A	407	0	3	4	0	119	533
M	427	57	46	6	0	57	593
C	1	80	47	1	5	22	156
CE	0	5	3	0	0	0	8
AMC	0	0	8	0	0	0	8
Cause of death							
Gastric cancer	32	1	6	0	0	2	41
Other cancer	25	12	7	1	1	5	51
Benign disease	60	9	17	2	0	10	98
Within 30 days	4	0	1	0	0	0	5
Unknown	65	13	19	2	3	9	111
Alive in 2004	649	107	57	6	1	172	992

**Fig. 1** Survival curves of patients who underwent DG, PG, TG, wedge-resection, resection of the rest stomach, and EMR. DG: distal gastrectomy, PG: proximal gastrectomy, TG: total gastrectomy, EMR: endoscopic mucosal resection

Aug. 1975-Oct.1989

Nov. 1989-Dec.2001

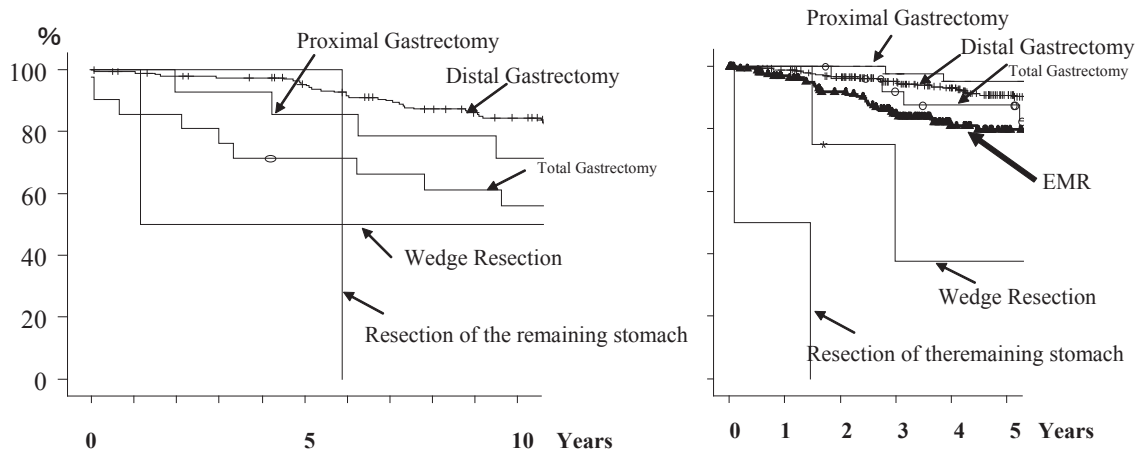


Fig. 2 Survival curves of the mucosal cancer patients during July 1975 to April 1989 and those during May 1989 to December 2001, who received DG, PG, TG, wedge-resection, resection of the rest stomach and EMR.

Aug. 1975-Oct.1989

Nov. 1989-Dec.2001

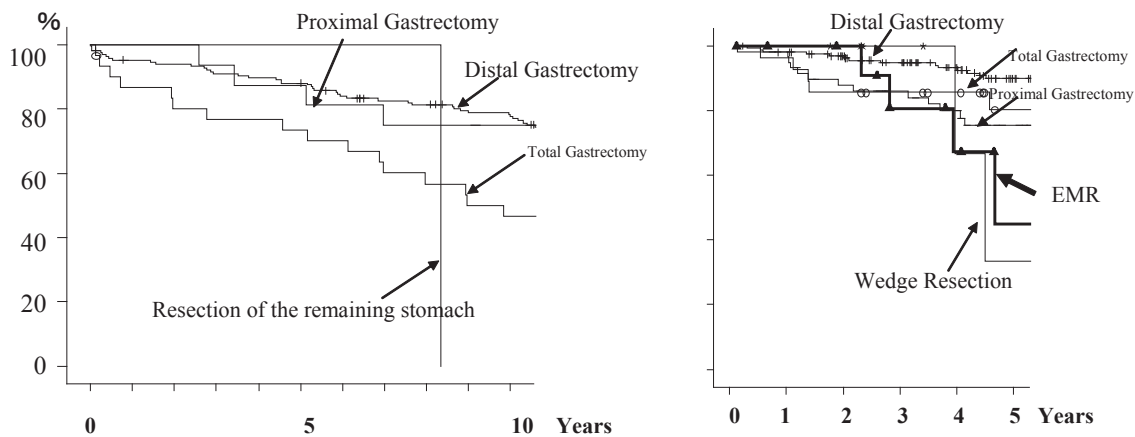


Fig. 3 Survival curves of the submucosal cancer patients during July 1975 to April 1989 and those during May 1989 to December 2001, who received DG, PG, TG, wedge-resection, resection of the rest stomach and EMR.

DG, PG, TG, wedge-resection, resection of the rest stomach and EMR during May 1989 to December 2001 were 90.8%, 95.2%, 87.6%, 37.5%, 0%, 79.9%, respectively. There were significant differences between DG and wedge-resection, resection of the rest stomach and EMR (log rank test, $p=0.0002$, $p<0.00001$, and $p=0.002$, respectively).

Fig. 3 showed the survival curves of the submucosal cancer patients during July 1975 to April 1989 and those during May 1989 to December 2001, who received DG, PG, TG, wedge-resection, resection of the rest stomach and EMR. Ten-year survival rates of patients receiving

DG, PG, and TG during July 1975 to April 1989 were 77.6%, 75.0%, and 46.7%, respectively. There were significant differences between TG and DG (log rank test, $p<0.00001$), PG and TG (log rank test, $p=0.0448$). Five-year survival rates of patients receiving DG, PG, TG, wedge-resection, and EMR during May 1989 to December 2001 were 90.0%, 75.5%, 80.4%, 33.3%, 0%, 49.9%, respectively. There were significant differences between DG and PG, TG, and EMR (log rank test, $p=0.0037$, $p=0.0026$, $p=0.0157$, and $p=0.0004$, respectively).

Fig. 4 showed the survival curves of the differenti-

Aug. 1975-Oct.1989

Nov. 1989-Dec.2001

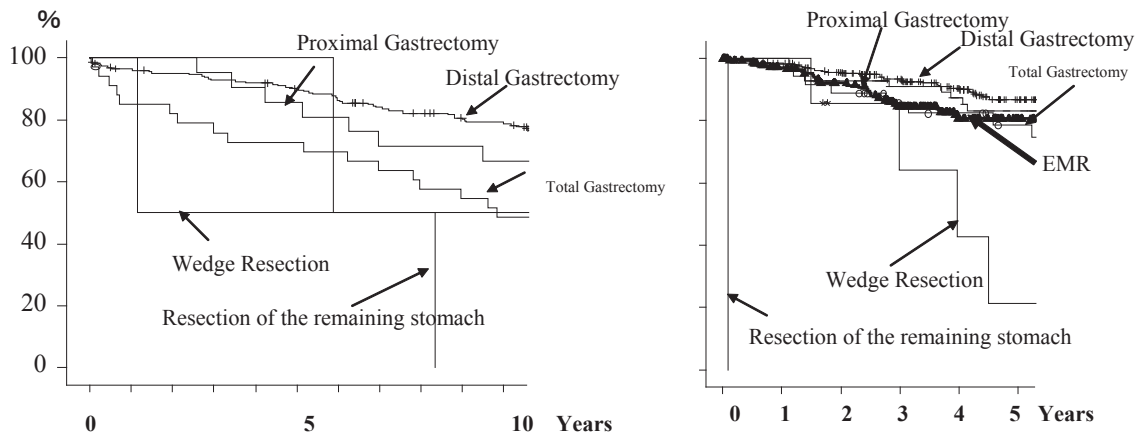


Fig. 4 Survival curves of the differentiated adenocarcinoma patients during July 1975 to April 1989 and those during May 1989 to December 2001, who underwent DG, PG, TG, EMR and wedge resection and resection of the rest stomach.

Aug. 1975-Oct.1989

Nov. 1989-Dec.2001

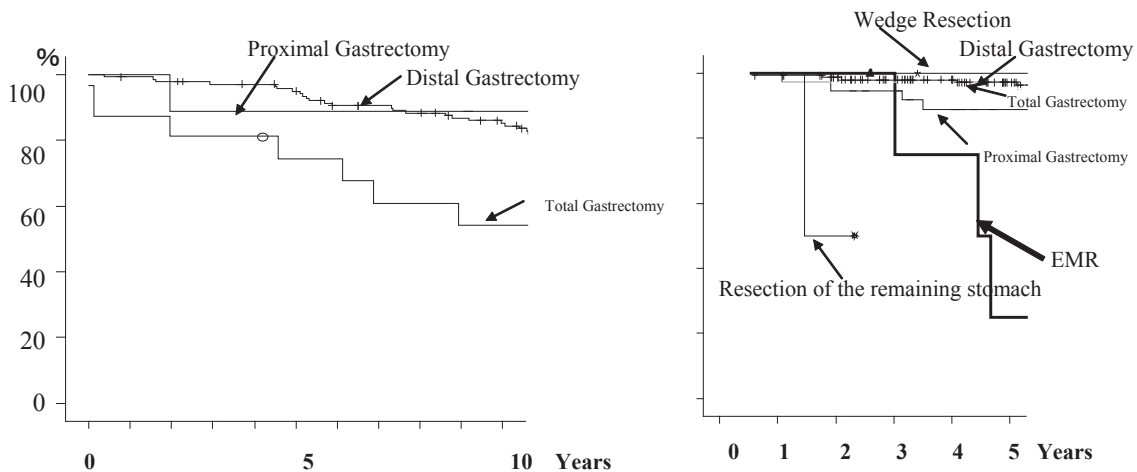


Fig. 5 Survival curves of the undifferentiated adenocarcinoma patients during July 1975 to April 1989 and those during May 1989 to December 2001, who underwent DG, PG, TG, EMR and wedge resection and resection of the rest stomach.

ated adenocarcinoma patients during July 1975 to April 1989 and those during May 1989 to December 2001, who underwent DG, PG, TG, EMR and wedge resection and resection of the rest stomach. Ten-year survival rates of patients receiving DG, PG, and TG during July 1975 to April 1989 were 78.7%, 66.7%, and 48.5%, respectively. There were significant differences between TG and DG (log rank test, $p < 0.00001$). Five-year survival rates of patients receiving DG, PG, TG, wedge-resection, and EMR during May 1989 to December 2001 were 86.8%, 83.0%, 78.7%, 21.4%, 0%, 80.8%, respectively. There were significant differences between DG and PG, TG,

and EMR (log rank test, $p = 0.0114$, $p = 0.0001$, $p < 0.0001$, and $p = 0.045$, respectively).

Fig. 5 showed the survival curves of the undifferentiated adenocarcinoma patients during July 1975 to April 1989 and those during May 1989 to December 2001, who underwent DG, PG, TG, EMR and wedge resection and resection of the rest stomach. Ten-year survival rates of patients receiving DG, PG, and TG during July 1975 to April 1989 were 85.2%, 88.9%, and 54.2%, respectively. There were significant differences between TG and DG (log rank test, $p = 0.0247$). Five-year survival rates of patients receiving DG, PG, TG, wedge-resection, and EMR

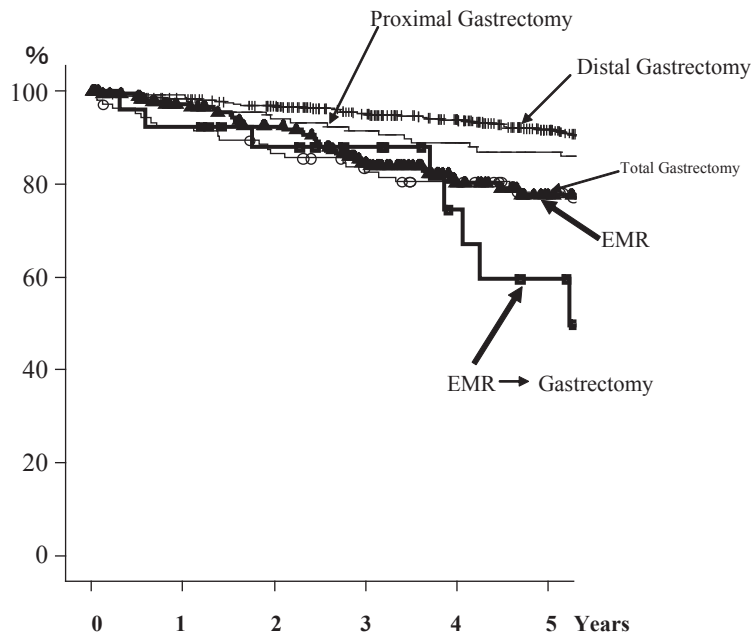


Fig. 6 Survival curves of patients receiving EMR alone, and gastrectomy after EMR, and those with DG, PG, and TG.

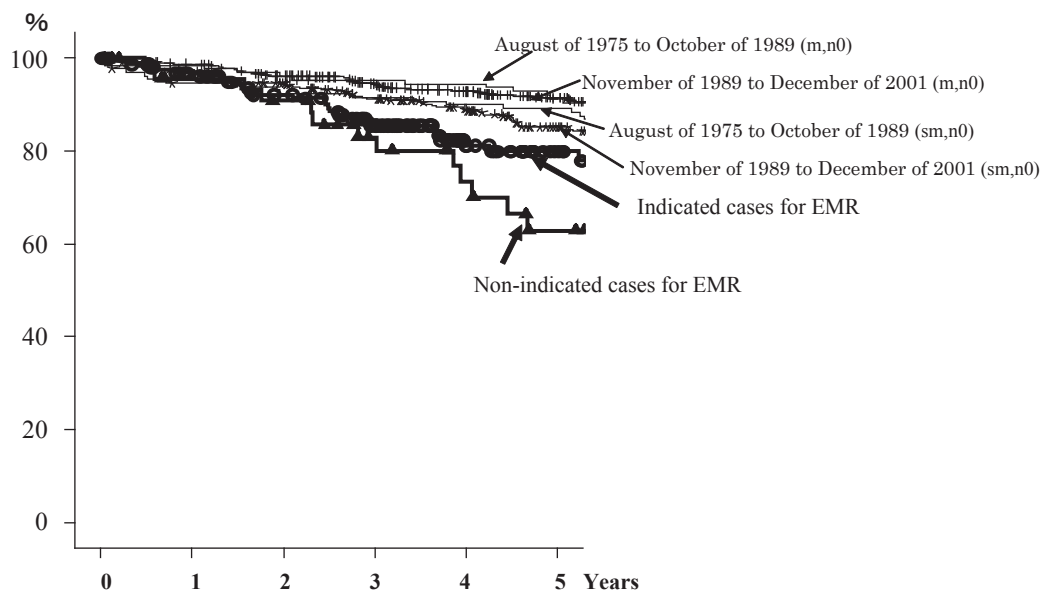


Fig. 7 Survival curves of the patients classified by the criteria of the Japanese Gastroenterology Endoscopy Society in comparison with the mucosal or submucosal cancer patients during July 1975 to April 1989 and during May 1989 to December 2001.

during May 1989 to December 2001 were 97.3%, 88.9%, 94.4%, 100%, 0%, 25.0%, respectively. There were significant differences between DG and TG, resection of the rest stomach and EMR (log rank test, $p=0.0026$, $p<0.0001$, and $p<0.0001$, respectively).

Fig. 6 showed the survival curves of patients receiving EMR alone, and gastrectomy after EMR, and those with DG, PG, and TG. Five-year survival rates of patients receiving EMR alone, and gastrectomy after EMR, and those with DG, PG, and TG, were 77.7%, 59.5%, and 91.6%, 87.0%, and 78.2%, respectively. There were

significant differences between EMR and DG (log rank test, $p<0.0001$), between gastrectomy after EMR and DG and PG (log rank test, $p<0.0001$, $p=0.007$, respectively), between TG and DG and PG (log rank test, $p<0.0001$, $p=0.0058$, respectively), and between DG and PG (log rank test, $p=0.0424$).

Fig. 7 showed the survival curves of the patients classified by the criteria of the Japanese Gastroenterology Endoscopy Society in comparison with the mucosal or submucosal cancer patients during July 1975 to April 1989 and during May 1989 to December 2001. Five-year

survival rates of patients receiving indicated EMR, and no-indicated EMR were 80.0% and 62.8%, respectively. While, patients of mucosal cancer with no lymph node metastasis during July 1975 to April 1989 and May 1989 to December 2001 were 91.2% and 91.4%, respectively, and those of submucosal cancer without lymph node metastasis during July 1975 to April 1989 and May 1989 to December 2001 were 89.1% and 85.1% respectively. There were significant differences between patients of indicated EMR and those of mucosal cancer during July 1975 to April 1989 and May 1989 to December 2001 (log rank test, $p=0.0214$ and $p=0.0018$, respectively), and between those of no-indicated EMR and those of both mucosal and submucosal cancer during July 1975 to April 1989 and May 1989 to December 2001 (log rank test, $p<0.0001$, $p=0.0008$, $p<0.0001$ and $p=0.0018$, respectively), between those of mucosal cancer during July 1975 to April 1989 and those of submucosal cancer during May 1989 to December 2001 (log rank test, $p=0.021$), and those of mucosal and submucosal cancer during May 1989 to December 2001 (log rank test, $p=0.023$).

Discussion

In this study, we showed that EMR treatment for early gastric cancer was not so better outcome than the traditional gastrectomy, especially distal and proximal gastrectomy, as we expected, even though compare to the outcome of the period when we did undergo gastrectomy for all gastric cancer patients whenever they had severe preoperative complications. These data was similar after analysis the data which fit to the Japanese EMR criteria treatment. We also want to point out that the outcome of patients receiving gastrectomy after EMR showed poorer survival than those receiving EMR. We have already reported that the patients who underwent lesser resection of the stomach showed better outcome than those who underwent total gastrectomy according to the restriction of diet³⁾.

From the consideration of our experience and the data shown here, there may occurred some speculations; one is the adequate restricted diet effect from distal or proximal gastrectomy, not from total gastrectomy, that is, excessive diet group, and no diet effect from EMR as well as wedge resection of the stomach. Another is the effectiveness of lymph node dissection, that is, patients with undifferentiated adenocarcinoma may receive more effective than those with differentiated adenocarcinoma from this procedure. Moreover, we also previously reported that patients who underwent partial (distal or proximal) gastrectomy and those with duodenal passage showed higher CD4/8 ratio levels concomitant with higher levels of CD4+ cells and lower levels of CD8+ cells after the gastrectomy. These results showed more

advantage of partial (distal or proximal) gastrectomy than that of TG⁴⁾. And also proximal gastrectomy may prevent to occur the secondary cancers in the stomach, because the cancer caused to proximal gastric portion according to the ages in especially differentiated adenocarcinoma. We had also reported the advantage of both the preservation of the stomach and the duodenal food passage reconstruction³⁾. But, the precise mechanisms are unclear.

On the other hand, the conception of EMR was introduced by Ottenjann⁵⁾, that is, big particle biopsy in 1973, and by Martin⁶⁾, that is, lift and cut biopsy in 1976. But the Application of EMR in clinical setting developed in Japan⁷⁾, because the incidence of early gastric and colon cancer in Japan was higher than the West.

If the lymphatic spread has been ruled out as far as is possible, a reasonable approach in selected cases of intramucosal early gastric cancer would be local therapy with endoscopic mucosal resection, followed by careful histological examination of the resected specimen and further endoscopic follow-up. If, however, we can select the cases to do EMR, the outcome of the EMR was not better than the traditional gastrectomy.

There was no report about the patients' outcomes compared to the surgery in English articles. Tada⁸⁾ reported in Japanese journal in 1998 that 5-year survival rate was 85.3%, and 10-year survival rate was 84.5% compared the surgery 90.9% and 87.4% respectively, including other causes of death, while, there was no patients who died of primary cancer. As doctors well know the bias between patients receiving EMR in whom might include patients who had severe complicated diseases, such as heart, renal, respiratory, and brain failure and then they could not receive gastrectomy and gastrectomy in whom might not include severe complicated diseases, they think, consequently, patients who received gastrectomies had better outcomes than patients who received EMR. This study showed the 10-year survival rates of patients who received gastrectomy in both period between 1974-1985 and 1986-present were the same, and were also significantly better than that of patients who received EMR in period between 1986-present. We agree that early gastric cancers have good outcome after gastrectomy. And also patients who received EMR that avoids surgery and its potential complications after gastrectomy, hope to have better quality of life (QOL) than surgery. But, there was no report about QOL comparing between traditional surgery and EMR treatment.

The indications were proposed by the Japanese Gastroenterology Endoscopy Society: (1) elevated-type intramucosal cancer less than 20 mm in size; (2) depressed-type mucosal cancer without ulceration less than 10 mm in size; (3) intestinal-type adenocarcinomas. Kojima *et al.* reviewed that in a review of 1832 cases reported in 12 series with appropriate follow-up, the sur-

vival rate was 99%, with only one death related to metastatic cancer⁹⁾.

Under these criteria, however, the data of patients receiving EMR shown present here was not better outcome than those receiving traditional therapy. EMR is a treatment for early gastric cancer available in most major Japanese institutions. Results from several series have been published (mainly in the Japanese literature), using different techniques, generally with good outcome in terms of curability. However, long-term follow-up results as well as the comparison between the EMR and traditional therapy in those reports are not clearly stated in most cases^{10,11)}.

In conclusion, although the outcome of patients who received EMR were not better than those who received partial (distal or proximal) gastrectomy, it is important to treat with minute and small cancer patients such as early cancer by endoscopy on the view point of patients' QOL. It is also important to discuss about what is doctors' aiming by doing EMR, to cure cancer or to care patients. Almost all doctors pray for cancer patients to have healthy life after treatment. From our results doctors who treat cancer patients by endoscopy, must guide to cancer patients about the important of both local therapy and the restriction of diet that is correlate to cure cancer and to patients' good health, respectively.

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