Endoscopic Resection for Undifferentiated-Type Early Gastric Cancer

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1. Introduction

Currently, endoscopic resection (ER) is the standard treatment for early gastric cancer (EGC), not only in Japan but also in other parts of the world. (Gotoda T et al., 2006)

A new endoscopic resection procedure, called endoscopic submucosal dissection (ESD), allows the direct dissection of the submucosa and has made en bloc resection of large intramucosal or ulcerated lesions feasible. However, at present, the indications for use of ER are limited to EGC without lymph node metastasis.

Gotoda et al. studied surgically resected specimens from EGC patients and decided upon the following four indication criteria for endoscopic resection of EGC without lymph node metastasis. (Gotoda T et al., 2000) (Fig 1)

1. differentiated intramucosal cancer without ulceration, regardless of size
2. differentiated intramucosal cancer with ulceration, 30mm or less in size
3. differentiated minute submucosal penetrative cancer (SM1), 30mm or less in size
4. undifferentiated intramucosal cancer without ulceration, 20mm or less in size

	Mucosal cancer				Submucosal cancer	
	UL(-)		UL(+)		SM1	SM2
Histology	≤20	20<	≤30	30<	≤30	any size
Differentiated	Guideline criteria for EMR	Extended criteria for ESD	Extended criteria for ESD	Extended criteria for ESD	Extended criteria for ESD	Extended criteria for ESD
Undifferentiated	Consider surgery *	Extended criteria for ESD	Extended criteria for ESD	Extended criteria for ESD	Extended criteria for ESD	Extended criteria for ESD

■ Guideline criteria for EMR □ Surgery
 ▨ Extended criteria for ESD ▨ Consider surgery *

Fig. 1. Extended criteria for endoscopic resection (Tumor size is shown in millimeters).

EMR: Endoscopic mucosal resection. ESD: Endoscopic submucosal dissection.

UL: ulcerative findings. SM: submucosal

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Expansion of the indications for ER to include undifferentiated-type EGC is not widely accepted at this time because undifferentiated-type EGC has been associated with higher rates of lymph node metastasis than has differentiated-type EGC. (Sano T et al.,1992 ; Yamao T et al.,1996)

Furthermore, it is sometimes difficult to delineate carcinomatous areas in cases where undifferentiated-type EGC is not exposed on the mucosa surface. (Ninomiya Y et al.,2000)

As a result, successful endoscopic resection is reportedly less common in patients with undifferentiated-type EGC compared to those with differentiated EGC. (Miyata M et al.,2000) To avoid invasive surgery, and thereby optimize the patient' s quality of life, it is important to expand the ER indication to include undifferentiated-type EGC in patients at a very low risk of lymph node metastasis.

Recently, several studies for undifferentiated-type EGC treated by endoscopic resection have been reported from different institutions. (Kim JH et al., 2009 ; Kang HY et al.,2010 ; Yamamoto Y et al.,2010) According to these reports, endoscopic resection for undifferentiated-type EGC was technically feasible and might be considered an alternative treatment modality.

In this review, we described the state of diagnostic and therapeutic endoscopy for undifferentiated-type EGC.

2. Undifferentiated-type EGC without lymph node metastasis

Because ER involves only local treatment without lymph node dissection, as a rule, it is performed only if lymph node metastases are not present.

In the study by Gotoda et al., the criteria for undifferentiated-type EGC without lymph node metastasis was intramucosal cancer without ulceration and a diameter of no more than 20mm (expanded-indication lesion). (Gotoda T et al.,2000)

However, this category of tumor was diagnosed in only 141 cases, and the 95% confidence interval for the frequency of positive lymph node metastases was 0-2.6%. This corresponds to a 5-year survival rate worse than the 99% associated with surgically resected intramucosal gastric carcinoma. Therefore, expansion of the indications for ER to include undifferentiated-type EGC was not widely accepted at that time.

Recently, Hirasawa et al. added to Gotoda's findings, by reporting on cases of undifferentiated-type EGC resected at their institutions over the past 9 years; they reported the lymph node metastasis rate and the validity of ER for undifferentiated-type EGC. (Hirasawa T et al.,2009) In the study, the number of expanded-indication lesion reached 310, and no lymph node metastasis was found in any of these cases. (Table 1)

Tumor size	LNM rate(%); UL(-) and LVI(-)
≤ 10 mm	0.0 (0/105)
11-20 mm	0.0 (0/205)
21-30 mm	1.9 (3/162)
≥ 31 mm	5.2 (13/249)
Total	2.2 (16/721)

Table 1. Lymph node metastasis by tumor size without UL and LVI in undifferentiated-type intramucosal EGC LNM: lymph node metastasis LVI: lymphatic-vascular capillary involvement UL: ulcerative findings

Thus, the 95% confidence interval decreased to 0-0.96%, with an upper limit of 1% or less. Therefore, it is suggested that the expanded-indication lesion of undifferentiated-type EGC could be considered suitable for curative ER due to the negligible risk of lymph node metastasis.

Several studies have proved that none of the cases of surgically resected expanded-indication lesions was associated with positive lymph nodes. (Ha TK et al.,2008 ; Li C et al.,2008 ; Li H et al.,2008 ; Ye BD et al.,2008 ; Kunisaki C et al.,2009 ; Li H et al.,2010)

However, even if the lesion met the criteria for expanded-indication lesion pathologically, in the previous study, some lesions with lymph node metastasis were reported. In three studies of surgically resected undifferentiated-type EGC that were 20mm or smaller in diameter and had neither ulceration nor lymphovascular invasion, a few were found to have metastasized. Lymph node metastases were found by Abe et al. in two cases with 10-mm or 12-mm lesions, (Abe N et al.,2004) by Nasu et al. in one case with a 13-mm lesion, (Nasu J et al.,2006) and by Park et al. in one case with a 17-mm lesion. (Park YD et al.,2008)

Even though the expanded-indication lesions of undifferentiated-type EGC have a very low risk of lymph node metastasis according to the report of Hirasawa et al, we should remain aware of the fact that a few of the expanded-indication lesion cases may have lymph node metastases.

What kind of mechanism would permit such a lesion to metastasize to the lymph nodes?

In normal gastric mucosa, lymphatic vessels are not found in the upper and middle part of the lamina propria; they exist in the deep lamina propria adjacent to the muscularis mucosa.

These morphologic findings correlate with clinicopathological observations on early gastric cancer. The particularly low incidence of lymph node metastases in the subtype of early gastric cancer that remains confined to the mucosa may be explained by the rarity of lymph capillaries in the mucosa. (Lehnert T et al.,1985 ; Listrom MB et al.,1987)

Sako et al. studied the distribution of lymphatic vessels in the gastric wall by immunostaining for D2-40. (Sako A et al., 2006) The densest distribution of lymphatic vessels was seen in the muscularis mucosa layer. If cancer cells reached the muscularis mucosa layer, they might have the greatest chance of invading the lymphatic vessels.

The morphological detection of intralymphatic tumor cells might be more difficult in undifferentiated-type EGC than differentiated-type EGC. The reason for this was presumed to be that undifferentiated-type EGC are often associated with a loss of glandular formation in the gastric wall, and the cancer cells may be more scattered in the lymphatic vessels.

Therefore, it is possible that if undifferentiated-type EGC reached the deep layer of the mucosa or the muscularis mucosa, the cancer cell could metastasize to the lymph node without invading the general lymphatic system.

However, it is noteworthy that no case with expanded-indication lesions of undifferentiated-type EGC less than 10mm in diameter had lymph node metastases. ER is therefore indicated in such lesions.

We suggest that ER should be used for the treatment of expanded-indication lesions of undifferentiated-type EGC in order to avoid unnecessary invasive surgery and optimize the quality of life.

3. The characteristics of expanded-indication lesion of undifferentiated-type EGC

Most patients with EGC treatable using ER have presented with no cancer related symptom: they have undergone an endoscopy because of symptoms of gastritis or esophagitis, and the cancers have been diagnosed incidentally.

Because an undifferentiated-type EGC indicated for ER has a diameter less than 20mm, it is important for an endoscopist to fully understand the endoscopic finding of such a lesion.

We performed a retrospective analysis of 60 patients who had histologically expanded-indication lesions of undifferentiated-type EGC in whom an ESD was performed at the Cancer Institute Hospital between March 2005 and August 2009. The patient characteristics and the endoscopic findings are shown in Table 2.

mean age $\pm$ SD (range)	58.3 $\pm$ 10.8 (33-78)	Tumor size	
sex		<10mm	28 (47%)
M	24 (40%)	10mm $\leq$	32 (53%)
F	36 (60%)	Histology	
Tumor location		sig	40 (67%)
L	12 (20%)	por	20 (33%)
M	45 (75%)	Tumor size and histology	
U	3 (5%)	<10mm (n=28)	
Gross type		sig	22 (79%)
flat	11 (18%)	por	6 (21%)
depressed	49 (82%)	10mm $\leq$ (n=32)	
lesion color		sig	18 (56%)
reddish	8 (13%)	por	14 (44%)
discolored	52 (87%)	H.pylori infection	
		negative	10 (17%)
		positive	50 (83%)

Table 2. Patient characteristics (n=60)

The mean age of the patients was 58.3 $\pm$ 10.8 years (range, 33-81 years), and number of male and female patients was 24 (40%) and 36 (60%) respectively.

The locations of lesions were as follows: lower third of stomach in 12 cases (20%); middle third in 45 cases (75%); upper third in 3 cases (5%).

Regarding the gross type, 11 lesions (18%) were flat, and 49(82%) were depressed, and regarding the tumor color, 52 (87%) were discolored, and 8 (13%) were reddish. Twenty-eight lesions (47%) were less than 10mm in diameter, and 32(53%) were larger than 10mm.

Regarding the histological findings, 40(67%) were signet ring cell carcinoma, and 20(33%) were poorly-differentiated adenocarcinoma.

Regarding the association between tumor size and histological finding, 22 of 28 lesions (79%) less than 10mm in diameter were histologically signet ring cell carcinoma, 18 of 32 lesions (56%) greater than 10mm in diameter were poorly-differentiated adenocarcinoma; lesions greater than 10mm in diameter frequently showed poorly-differentiated adenocarcinoma.

With respect to *Helicobacter pylori* (HP) infection, 17 of 60 patients (17%) showed no HP infection and no atrophic change in the gastric mucosa, these 17 patients were negative for serum HP antibody and serum pepsinogen; undifferentiated-type EGC was found in the patients who were negative for HP infection.

In summary, undifferentiated-type EGC tended to be found more frequently in females than in males, located in the middle third of the stomach, be 'discolored' in appearance, and was most frequently of the depressed type. (Fig 2)

a: Routine observation: A discolored area with biopsy scar in the central was located on the lower-body lesser curvature.. (yellow arrows)

b: Indigo carmine spraying: Dye spraying revealed a discolored lesion with depression. (yellow arrows).

c: Narrow band imaging with magnifying view : NBI showed irregular vascular pattern in the depressed lesion. (yellow arrows)

d: Resected specimen: specimen size 28×23 mm, tumor size 13×9 mm, type 0-IIc, sig, UL(-), pM, ly0, v0, LM(-), VM(-).

e: HE staining: Tubular structure in the lesion was not recognized.

f: PAS staining: Signet-ring cells with PAS staining positive were observed in the middle layer of the mucosa.(yellow arrows)

Fig. 2. Undifferentiated EGC met expand-indication criteria for ESD.

In the development of gastric cancer, it was very interesting that undifferentiated-type EGC was even found in the patients with no evidence of HP infection. (Fig 3)

In a depressed-type EGC, encroachment of the border is one important malignant sign to look for in endoscopic findings. (Oohara et al.,1984 ; Fujii T et al.,1994) However, Takahashi et al. reported that encroachment of the border was found in only 20% patients with undifferentiated-type EGC with diameters less than 10mm. (Takahashi H et al.,2009)

To diagnose undifferentiated-type EGC treatable by ER, an endoscopist should take care when performing an endoscopic examination in order not to overlook a depressed and discolored lesion with no encroachment of the border.

- a: Routine observation: A discolored area was located on the lower-body anterior wall. (yellow arrows)
This patient had not *H.pylori* infection
- b: Closed view: The border of discolored area was clearly distinguished from the adjacent mucosa.
- c: Indigo carmine spraying: Dye spraying revealed a discolored lesion without depression. (yellow arrows). The macroscopic appearance suggested type 0-IIb early gastric cancer.
- d: Resected specimen: specimen size 28x23 mm, tumor size 13x9 mm (red line), type 0-IIc, sig, UL(-), pM, ly0, v0, LM(-), VM(-).
- e: HE staining: Tubular structure in the middle layer of the lesion was not recognized.
- f: PAS staining: Signet-ring cells with PAS staining positive were observed in the middle layer of the mucosa. (yellow arrows)

Fig. 3. A case of undifferentiated EGC without *H.pylori* infection.

4. Diagnosis of tumor margin and narrow band imaging for undifferentiated-type EGC

Narrow band imaging (NBI) is a new electronic endoscopy system ideally suited to the observation of surface structures, including capillaries. With NBI, short wavelength light radiated through a narrow band filter is strongly absorbed by hemoglobin, thereby allowing surface vascular structures to be distinctly visualized. (Gono K et al., 2004)

The NBI-magnifying endoscopy is capable of predicting the histological characteristics of gastric cancer lesions in not only well-differentiated-type EGC but also in undifferentiated-type.

Nakayoshi et al. reported that microvascular structures can be observed using the NBI magnifying endoscopy, with a fine network pattern visible in well-differentiated-type EGC, and, in contrast, a corkscrew pattern in undifferentiated-type EGC. (Nakayoshi T et al., 2004) Taken together, these findings suggest that, if a discolored depressed lesion without encroachment found by conventional endoscopy showed a corkscrew pattern by NBI, the lesion is probably undifferentiated-type EGC.

It is well known that it is more difficult to determine the lesion margin in undifferentiated-type EGC than in well-differentiated-type. In some cases of undifferentiated-type EGC, the lesion margin estimated macroscopically with the naked eye differs from that determined by pathology. (Ninomiya et al.,2000)

This difference occurs when the tumor extends along the proliferative zone in the middle layer of the mucosa, leaving normal ducts covering the superficial mucosa. When this extension of cancer cells along the proliferative zone occurs, it is difficult to diagnosis the area of the lesion, even using NBI-magnifying endoscopy. To achieve a more accurate diagnosis, circumferential biopsies of the lesion should be done in all cases of undifferentiated-type EGC.

Recently, we have reported that the width of the proliferative zone in 40 cases of expanded-indication lesion of undifferentiated-type EGC ranged from 0 to 2,390 μ m (average 605.5 μ m). (Sawada S et al.,2010) (Fig.4)

In no cases was the width of the proliferative zone over 3mm. (Table 3)

From these results, we recommend that markings around a lesion should be placed 5mm beyond the endoscopically determined lesion margin, and mucosal incisions should be made outside these markings for ER of undifferentiated-type EGC.

M : mucosa MM : muscularis mucosa SM : submucosa

Fig. 4. Width of proliferative zone

0-1,000 μ m	28 (70)
1,001-2,000 μ m	11 (27.5)
2,001-3,000 μ m	1 (2.5)
Total	40 (%)
n=40, mean=605.5 μ m	

Table 3. Width of proliferative zone (0-II c type undifferentiated-type intramucosal EGC)

5. Therapeutic outcomes of ESD of undifferentiated-type EGC

Endoscopic resections for EGD were divided into two types of procedures, endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). There are several EMR procedures, including the strip biopsy method (Okazaki Y et al.,1991), double channel method (Takekoshi T et al.,1986), EMR-cap method (Takeshita et al.,1997) These EMR

procedures, however, cannot be used for the en bloc resection of lesions larger than 2cm. (Hyun DH et al.,2003)

On the other hand, ESD techniques can make en bloc resection of large lesions or ulcerated lesions feasible. It is important for the success of the ER of undifferentiated-type EGC that the histological findings are evaluated in detail. If the lesion is non-curative pathologically, the patient must undergo additional surgical resection of the stomach. Therefore, ER of undifferentiated-type EGC should be performed with an en bloc resection by ESD procedure.

We reviewed 58 patients with preoperatively diagnosed undifferentiated-type EGC (expanded-indication lesion) who underwent ESD at the Cancer Institute Hospital between September 2003 and August 2008. 9 We carried out ESD using the insulation-tipped diathermic knife method, and glycerol or hyaluronic acid as the local injection material.

The therapeutic outcomes of ESD are shown in Table 4.

The mean diameter of resected specimens was 30mm (range, 15-48mm), the mean diameter of lesions was 11mm (range, 2-28mm), the median operation time was 70 min (range, 23-340 min), the en bloc resection rate was 98 % (57/58 patients), the complete en bloc resection (R0 resection) rate was 90 % (52/58 patients), the curative resection rate was 79 % (46/58 patients).

Bleeding complications occurred in five cases (8.6 %). No cases required blood transfusion or surgery. Perforation occurred in two cases (3.4%), both of which were conservatively and successfully treated by clipping closure. The mean hospital stay was 6.7 days (range, 4-14 days)

Specimen diameter (mm), mean (range)	30 (15-48)
Tumor diameter (mm), mean (range)	11 (2-28)
Operation time (minutes), median (range)	70 (23-340)
One-piece resection rate, n/N (%)	57/58 (98%)
Complete resection rate, n/N (%)	52/58 (90%)
Curative resection rate, n/N (%)	46/58 (79%)
Accurate preoperative diagnosis, n/N (%)	47/58 (81%)
Complications, n (%)	
Bleeding	5 (8.6%)
Perforation	2 (3.4%)
Hospital stay (days), mean (range)	6.7 (4-14)

ESD: Endoscopic submucosal dissection

EGC: Early gastric cancer

Table 4. ESD for undifferentiated-type EGC treatment results (N=58)

Pathological examination revealed that expanded-indication lesions were present in 47 cases and non-indication lesions in 11. The therapeutic outcomes were compared between the two groups, as shown in Table 5.

	Expanded-indication lesions (N=47)	Non-indication lesions (N=11)	P value
Specimen diameter (mm), mean (range)	29 (15-48)	33 (15-45)	0.2
Tumor diameter (mm), mean (range)	8.9 (2-18)	18 (8-28)	<0.01
Operation time (minutes), median (range)	65 (23-340)	80 (26-250)	0.55
One-piece resection rate, n/N (%)	47/47 (100%)	10/11 (91%)	0.42
Complete resection rate, n/N (%)	46/47 (98%)	6/11 (55%)	<0.01
Curative resection rate, n/N (%)	46/47 (98%)	0/11 (0%)	
Complications, n (%)			
Bleeding	5 (11%)	0	0.59
Perforation	2 (4.3%)	0	0.82
Hospital stay (days), mean (range)	6.6 (4-14)	7.2 (5-9)	0.3

Table 5. ESD for undifferentiated type EGC treatment results by lesion group (N=58)

With the limited expanded-indication lesions, the mean diameter of the resected specimens was 29mm (range, 15-48mm), the mean diameter of lesions was 8.9mm (range, 2-18mm), the median operation time was 65 min (range, 23-340 min), the en bloc resection rate was 100 % (47/47 patients), the complete en bloc resection rate was 98 % (46/47 patients), and the curative resection rate was 98 % (46/47 patients).

From these results, it can be seen that ESD of expanded-indication lesions for undifferentiated-type EGC was associated with good therapeutic outcomes.

However, non-curative resection was pathologically identified in 12 (21%) of the 58 patients. Eleven of the 12 non-curative resection cases had non-indication lesions. The reasons for incurability were the presence of submucosal invasion in seven cases (12 % of 58 patients), tumor diameter of 21mm or more in five (8.6%), and the presence of ulcer scarring in two (3.4 %); some cases had more than one reason.

The most common factor responsible for non-curative resection was incorrect diagnosis of the depth of invasion. (Table 6)

Factors	n (%)†
Submucosal invasion	7 (12%)
Tumor diameter >20 mm	5 (8.6%)
Ulcer findings	2 (3.4%)
Lymphatic-vascular involvement	2 (3.4%)

*Some patients had more than one causative factor.

† Percentages were calculated based on overall population (N=58).

Table 6. Factors responsible for non-curative resection of non-indication lesions (N=11)*

Six of the seven patients who were found to have submucosal invasion had undergone EUS that resulted in a diagnosis of intramucosal carcinoma.

It has been reported previously that EUS correctly diagnosed the depth of invasion of EGC in 64-78% of cases, and the correct diagnosis rate was lower in cases of undifferentiated-type compared to differentiated-type. (Akahoshi K et al.,1998 ; Hizawa K et al.,2002) Although more accurate diagnosis of the invasive depth is necessary, the currently available assessment methods have limitations in their precision. (Kim JH et al.,2007)

In terms of the technological aspects of ESD, resectable expanded-indication lesions of undifferentiated-type EGC are less than 20mm in diameter and have no ulceration, the ESD procedures are easier than for lesions with diameters greater than 20mm or for ulcerated differentiated-type EGC. Therefore, we consider that the ideal method for diagnosing the invasion depth might be to first carry out ESD followed by pathological examination of resected specimens.

However, if this diagnostic ESD determines that a tumor diameter exceeds 20mm, it is probable that ESD will result in non-curative resection, so more precise preoperative diagnosis of the lesion area using circumferential biopsies is essential.

6. Conclusion

Endoscopic resection of differentiated-type EGC is now standard treatment not only in Japan but also in other parts of the world. Undifferentiated-type EGC has a high rate of lymph node metastasis compared with differentiated-type EGC, and endoscopic resection of undifferentiated-type EGC remains controversial.

However, if the tumor is detected at an early stage and meets the criteria for expanded-indication lesion of undifferentiated-type EGC, then the lymph node metastasis is very rare. We propose that endoscopic resection should be performed on such lesions to avoid unnecessary invasive surgery and optimize the quality of life. In this review, we have described our therapeutic outcomes of endoscopic resection for undifferentiated-type EGC.

An interesting result amongst our cases was the observation that some patients who were *H. pylori* negative had undifferentiated-type EGC. The rate of *H. pylori* infection is predicted to decrease in the future. We should take care in the management of cases of undifferentiated-type EGC without *H. pylori* infection.

It is necessary to study further cases, with a longer follow up period, to prove the validity of the concept of endoscopic resection of undifferentiated-EGC which we have proposed here.

We hope that multicenter, prospective studies will be carried out to assess further this expanded-indication for ER of undifferentiated-type EGC.

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Endoscopy has had a big role in the development of modern gastroenterology. Modern endoscopy will certainly be more therapeutic. It started with endoscopic hemostasis and polypectomy, than beginning of the 1970's with the advent of endoscopic sphincterotomy extended to biliopancreatic pathology and has a huge impact in this difficult pathology. Plastic stents made the first steps in endoscopic palliation of neoplastic jaundice, metallic stents, covered or uncovered are better for biliary palliation and can be used also for palliation neoplastic obstruction at different levels of the digestive tube. Resection of digestive tumors has evolved now to sub-mucosal resection, looking to have one-piece complete resection. Interventional endoscopy is now very complex and takes a lot of time for endoscopists to learn properly these techniques. This book is a very good up-to-date overview of new techniques of interventional endoscopy for those who want to learn or develop their knowledges in this field.

How to reference

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