

否定されるものではない。しかしながら、費用対効果を考慮すると、必ずしも導入を推進するものではないという結果が得られた。

今後モデルのさらなる改善を行い、結果の頑健性を確認していく必要がある。

#### E. 結論

乳がん・肺がん・甲状腺がん・大腸がんに限って PET 検診の費用効果分析を行うと、大腸がんのみ費用効果的であることが示唆された。

#### F. 健康危険情報

なし

#### G. 研究発表

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#### H. 知的所有権の取得状況

1. 特許取得  
なし
2. 実用新案登録  
なし
3. その他  
なし

新しい診断機器の検診への応用とこれらを用いた

診断精度の向上に関する研究

平成20年度

### Ⅲ. 研究成果の刊行に関する 一覧表

## 研究成果の刊行に関する一覧表（平成20年度）

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# Indications for Endoscopic Submucosal Dissection of Early Gastric Cancers

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*Summary.* The accepted guideline at the present time for endoscopic mucosal resection (EMR) of early gastric cancer (EGC) is an intramucosal well-differentiated adenocarcinoma 20 mm or less ( $\leq 20$  mm) in diameter without ulceration. Recent advances in the endoscopic submucosal dissection (ESD) technique, however, now make it possible to resect en bloc larger intramucosal lesions as well as submucosal lesions with minute penetration  $\leq 500$   $\mu\text{m}$  (SM1), so expanded criteria for endoscopic resection of EGC have been proposed as follows: (1) intramucosal well-differentiated adenocarcinoma without ulceration regardless of lesion size; (2) intramucosal well-differentiated adenocarcinoma with ulceration  $\leq 30$  mm in diameter; and (3) SM1 well-differentiated adenocarcinoma  $\leq 30$  mm in diameter. ESD has been specifically developed for the en bloc resection of larger lesions, but it is considerably different and technically more difficult than EMR. The results so far have been highly encouraging, although long-term outcome data are still unavailable.

*Key words.* Endoscopic submucosal dissection (ESD), Endoscopic mucosal resection (EMR), Early gastric cancer, Lymph node metastasis

## Introduction

Endoscopic resection is a local resection technique that differs dramatically from surgery with lymph node (LN) dissection. Candidates for such endoscopic treatment are patients with lesions having a low risk or no risk of LN metastasis. The incidence of LN metastasis differs among digestive organs such as the esophagus, stomach [1], and colon. Any decision for surgery will depend on balancing the LN metastasis and surgical risks with the patient's expected quality of life after surgery.

Endoscopic resection for EGC is currently accepted as a standard treatment in Japan and is increasingly gaining worldwide acceptance [2]. Endoscopic resection is comparable in certain respects to conventional surgery with the advantages of being

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less invasive and more economical. The low incidence of LN involvement in certain stages of EGC means that curative results can be achieved using such local treatment in selected cases.

Endoscopic resection also enables complete pathological staging of EGC, which is critical because it allows stratification and refinement of further treatment. Patients with a low risk or no risk of LN metastasis, therefore, are ideal candidates for endoscopic resection relative to the operative risks associated with surgery and their reduced quality of life following such surgery.

The role of endoscopic resection in the management of EGC is the focus of this section.

## Definition and Approach to Early Gastric Cancer

EGC is defined as gastric cancer (GC) in which tumor invasion is confined to the mucosal or submucosal (SM) layer (T1 cancer), irrespective of LN status [3] other than in considering the adverse impact of LN metastasis on a particular patient's prognosis. Previously, gastrectomy with LN dissection had been the gold standard treatment in Japan for GC patients, even those with EGC. This radical surgery carries significant risks of morbidity and mortality, however, and is associated with a long-term reduction in the quality of life for those patients receiving such treatment.

Analyses of hundreds of thousands of pathology reports, past patient histories, and long-term survival rates from the National Cancer Center Hospital and other medical institutions in Japan have demonstrated that the 5-year cancer-specific survival rates for GC patients with intramucosal and SM lesions are 99% and 96%, respectively [4]. In patients with intramucosal GC, the incidence of LN metastasis is less than 3%, but the risk increases to approximately 20% when the cancer invades the SM layer. EGC patients with virtually no risk of LN metastasis have been identified by analyzing extensive data, and such patients, who conform to specific endoscopic and pathological criteria, are ideal candidates for endoscopic resection rather than surgery.

The primary advantage of endoscopic resection is its ability to provide complete pathological staging without the need for radical surgery. After endoscopic resection, pathological assessment of the depth of cancer invasion, the degree of differentiation of the cancer, and the extent of lymphatic-vascular invasion enables the risk of LN metastasis to be accurately predicted using published data on patients with similar findings [5]. The risks of LN metastasis and distant metastasis are then weighed in comparison with the risks of surgery.

Unfortunately, such precise staging cannot be as accurately achieved using any imaging technique presently available such as endoscopic ultrasound (EUS) or computed tomography (CT). EUS has been considered accurate for tumor depth staging, for example, but the accuracy rate in cases has been reported to vary from 80% to 90%. In addition, the accuracy of EUS reportedly decreases to less than 60% in difficult cases of tumor depth diagnosis. Any treatment plan based on EUS findings, therefore, potentially means that some patients will be subjected to unnecessary

surgery. Proper staging can only be accomplished through histological analysis achieved by performing an endoscopic resection.

## Indications for Endoscopic Resection of Early Gastric Cancer

Currently accepted indications for EMR of EGC include small intramucosal lesions of the differentiated type (Fig. 1) [6].

This guideline is based on the knowledge that larger-size lesions and undifferentiated type lesions are more likely to extend into the SM layer and thus have a higher risk of LN metastasis. In addition, en bloc resection of large lesions has oftentimes been too difficult technically until the more recent development of the ESD technique.

At present, the accepted indications for conventional EMR are (1) differentiated type elevated cancers  $\leq 20$  mm in diameter and (2) differentiated type small depressed lesions  $\leq 10$  mm without ulceration. All such lesions must be moderately or well-differentiated cancers confined to the mucosa and have no lymphatic or vascular involvement histologically.

Clinical observations have noted, however, that the present criteria for endoscopic resection may be too strict, leading to unnecessary surgery [3]. The currently accepted indications for endoscopic resection assumed conventional EMR as the primary treatment strategy. Recent advances in the ESD technique now make it possible, however, to resect larger intramucosal GC lesions and SM1 GC lesions, so expanded criteria have been proposed for endoscopic resection. The upper limit of the 95% confidence interval (CI) calculated from earlier studies, however, was too broad for clinical use because of small sample sizes.

Using a large database involving more than 5000 patients who underwent gastrectomy with meticulous R2 level LN dissection, Gotoda et al. [1] recently further defined the risk of LN metastasis in additional groups of EGC patients with increased certainty (Table 1). According to their intramucosal cancer findings, none of the 1230

| Depth \ Histology | Mucosal cancer |        |           |        | Submucosal cancer |          |
|-------------------|----------------|--------|-----------|--------|-------------------|----------|
|                   | UL(-)          |        | UL(+)     |        | SM1               | SM2      |
|                   | $\leq 20$      | $20 <$ | $\leq 30$ | $30 <$ | $\leq 30$         | any size |
| Differentiated    | ■              | □      | □         | □      | □                 | □        |
| Undifferentiated  | □              | □      | □         | □      | □                 | □        |

Guideline criteria for EMR
  Surgery

FIG. 1. Current guideline criteria for endoscopic mucosal resection (EMR) of early gastric cancer (EGC)

TABLE 1. Early gastric cancer (EGC) with no risk of lymph node metastasis.

| Criterion   | Incidence (%) | 95% CI  |
|---|---------------|---------|
| Intramucosal EGC<br>Differentiated adenocarcinoma<br>No lymphovascular invasion<br>Irrespective of ulcer findings<br>Tumor $\leq$ 30 mm in size | 0/1230 (0%)   | 0%-1.3% |
| Intramucosal EGC<br>Differentiated adenocarcinoma<br>No lymphovascular invasion<br>Without ulcer findings<br>Irrespective of tumor size         | 0/929 (0%)    | 0%-0.4% |
| Undifferentiated intramucosal cancer<br>No lymphovascular invasion<br>Without ulcer findings<br>Tumor $\leq$ 20 mm in size                      | 0/141 (0%)    | 0%-2.6% |
| Minute submucosal penetration (SM1)<br>Differentiated adenocarcinoma<br>No lymphovascular invasion<br>Tumor $\leq$ 30 mm in size                | 0/145 (0%)    | 0%-2.5% |

differentiated lesions  $\leq$ 30 mm in size was associated with LN metastasis regardless of ulceration (95% CI, 0%-0.3%). Similarly, none of the 929 differentiated lesions without ulceration was associated with LN metastasis regardless of lesion size (95% CI, 0%-0.4%).

As for SM invasive cancer, there was a significant correlation between tumors  $>$ 30 mm in size and lymphatic-vascular involvement with an increased risk of LN metastasis. In addition, those cancers penetrating deep into the SM layer were the most likely to be associated with regional LN metastasis. The subgroup of 145 histologically differentiated lesions  $\leq$ 30 mm in size with no lymphatic-vascular involvement and SM1 penetration as classified according to the Japanese Classification of Gastric Carcinoma, however, was entirely free of LN metastasis (95% CI, 0%-2.5%).

Last, none of the 141 undifferentiated histological lesions without ulceration  $\leq$ 20 mm in size was associated with a positive LN finding (95% CI, 0%-2.6%). The mortality of patients who have undergone standard gastrectomy with LN dissection at our hospital is 0.2% to 0.5%. Considering surgical mortality and the 99% 5-year survival rate for mucosal cancer, considerable controversy exists concerning the appropriate treatment strategy for patients with mucosal cancer consisting of the undifferentiated histology type. A recent report based on a large series has shown that EGC with signet-ring cell carcinoma has a low rate of LN metastasis, suggesting that mucosal cancer with signet-ring cell carcinoma could also be a candidate for less-invasive surgery [7].

These groups of patients were shown to have a low risk or no risk of LN metastasis, which is significant when considering the risk of mortality from surgery. The results of this study have facilitated the development of an expanded list of candidates suitable for endoscopic resection primarily using the ESD technique [8] (Fig. 2), because

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

FIG. 2. Proposed expanded criteria for endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) of early gastric cancer (EGC)

lesions covered by these proposed extended criteria for endoscopic resection would previously have been resected in a piecemeal fashion if treated by conventional EMR.

### Importance of En Bloc Resection

EMR has been successfully practiced in Japan for the past two decades for the removal of small EGC. Outcomes involving EMR of larger intramucosal carcinomas of the stomach, however, have been less favorable. Piecemeal resections required during the removal of larger lesions can lead to a higher risk of local recurrence and make it more difficult for pathologists to render precise depth and margin assessments.

The minimal risk of LN involvement in large EGC coupled with the potential curative role of endoscopic therapy, however, has provided the impetus for the development of a new technique of endoscopic resection to overcome the limitations associated with piecemeal resections. ESD was specifically developed to allow en bloc resections of even larger lesions [9]. An en bloc resected specimen provides proper orientation, sectioning, and margin assessment, resulting in improved pathological examination. Accurate histopathology is critical because the criteria for a curative endoscopic resection are based on careful assessment of the serial sectioning of a pathological specimen. The ESD technique also allows en bloc resections to be performed through fibrotic SM tissue, which is commonly found during resections of ulcerated EGC.

### Endoscopic Submucosal Dissection (ESD)

ESD for EGC has been explored since the early 1990s and is increasingly practiced throughout Japan. The popularity of the technique can be attributed to the technical ability to endoscopically remove large EGCs en bloc with less morbidity and mortality compared to the more invasive surgical alternatives.

ESD using a variety of specially created endoscopic knives has been developed for en bloc resection using a standard single-channel gastroscope (Fig. 3). This procedure has the major advantage of being able to achieve large and en bloc resections.

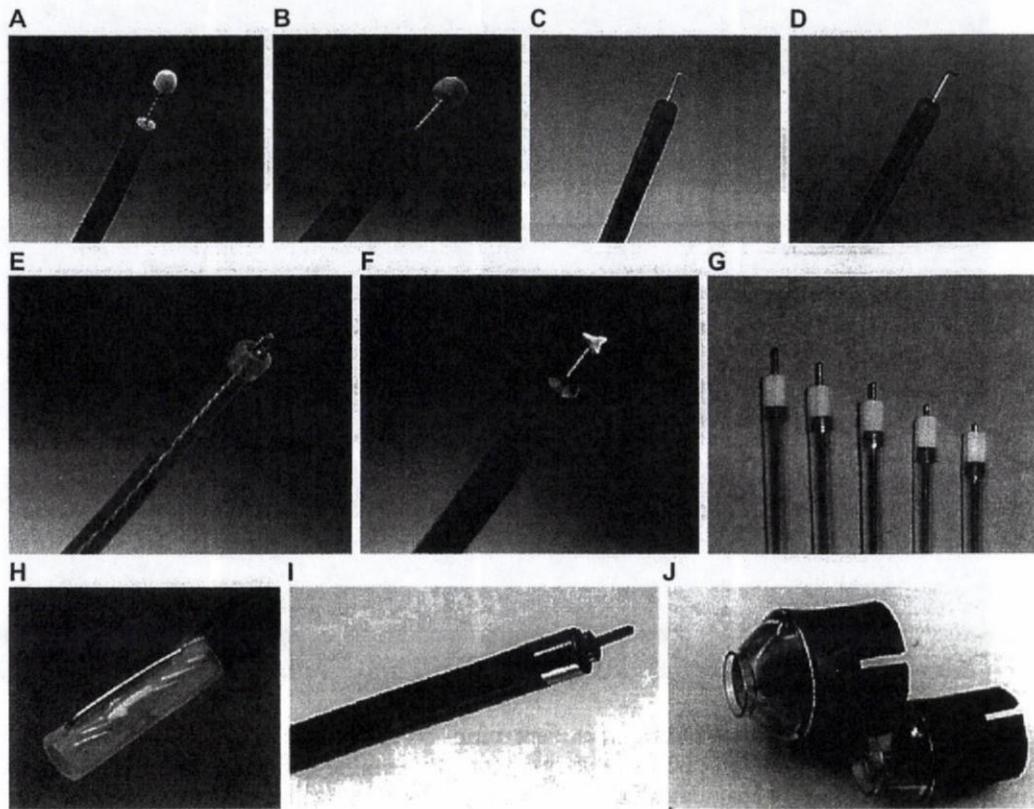


FIG. 3. Endoscopic devices for ESD. A Insulation-tipped surgical knife (IT knife) (KD-610L, Olympus Medical Systems). B Modified IT knife with three-pointed star blade (KD-611L, Olympus Medical Systems). C Needle knife (KD-1L-1, Olympus Medical Systems). D Hook knife (KD-620LR, Olympus Medical Systems). E Flex knife (KD-630L, Olympus Medical Systems). F Triangle-tipped knife (Olympus Medical Systems). G Flash knives with several needle lengths (Fujinon Toshiba ES Systems). H Mucosectomy (DP-2518, Pentax). I Bipolar needle knife (B-knife; Xemex). J Small-caliber tip transparent (ST) hood (DH-15GR, 15CR; Fujinon Toshiba ES Systems)

ESD consists of three steps: first, injecting solution into the SM layer to separate the lesion from the muscle layer; next, predetermined circumferential cutting of the mucosa surrounding the lesion; and, finally, dissection of the SM connective tissue under the lesion.

Marking the periphery of the lesion (Fig. 4A-C) is performed using a standard needle knife (or hook knife, flex knife, triangle-tipped knife, or flash knife) with a forced 20 W coagulation current (ICC200; ERBE, Tübingen, Germany). After injection with diluted epinephrine (1:100 000) to raise the SM layer, a small initial incision (Fig. 4D) to insert the tip of an insulation-tipped surgical knife (IT knife) into the SM layer is made by a standard needle knife in the 80 W ENDO-CUT mode with effect 3 (ICC200, ERBE).

Circumferential mucosal cutting at the periphery of the marking dots (Fig. 4E-G) is then performed using the IT knife in 80 W ENDO-CUT mode. A ceramic ball at the tip of the IT knife prevents perforation of the muscle layer. After completion of the

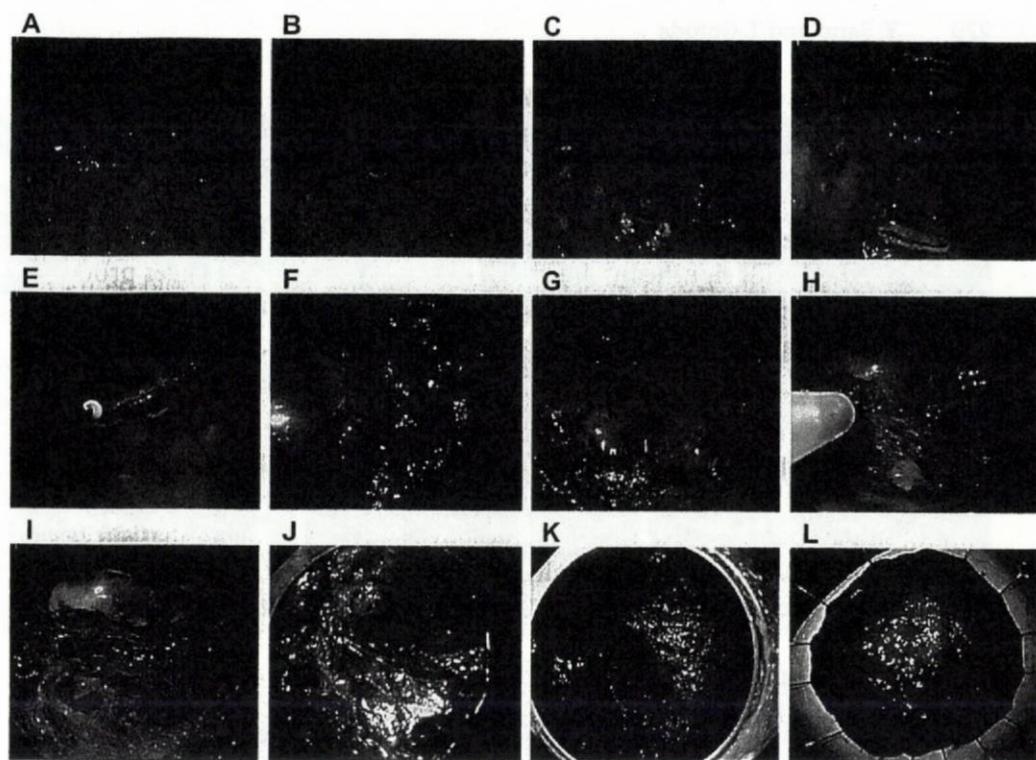


FIG. 4. ESD procedures. A Locally recurrent tumor on greater curvature of gastric antrum after piecemeal EMR. B Indigo carmine dye spray for determining tumor margin. C Markings made by needle knife with coagulation current. D Initial incision made using needle knife in ENDO-CUT mode after injection of diluted epinephrine. E Ceramic ball prevents perforation of muscle layer. F Mucosal cutting using IT knife in ENDO-CUT mode. G Circumferential mucosal cutting at periphery of marking dots. H Additional submucosal (SM) injection with diluted epinephrine after completing circumferential cutting. I Dissecting SM layer using IT knife in ENDO-CUT mode. J Attachment cap for stretching SM tissue. K Large ESD ulcer bed after complete en bloc resection without perforation. L Flattened periphery of ESD specimen using thin needles on plate

circumferential cutting, additional diluted epinephrine is injected into the SM layer (Fig. 4H).

The SM layer under the lesion is directly dissected (Fig. 4I) with the IT knife using a lateral movement. It is important to cut tangentially at the SM layer to avoid perforation. Indigo carmine dye previously injected into the SM layer helps to identify it. Additional diluted epinephrine can be injected into the SM at any time to raise and confirm the SM layer. An attachment cap (Olympus Medical Systems, Tokyo, Japan) is frequently used to provide traction for the resected specimen and help exfoliate the SM tissue (Fig. 4J). ESD can provide a large en bloc resection without size limitation (Fig. 4K). Finally, the resected specimen is retrieved using grasping forceps.

The ESD technique allows for the one-piece removal of ulcerated gastric lesions and the resection of recurrent EGC after an unsuccessful EMR. It was extremely difficult, if not impossible, to resect these lesions previously by conventional EMR

techniques because SM fibrosis prevented adequate lifting of the mucosal lesion by SM injection.

Despite requiring additional technical skill and involving a longer procedure time, the ESD technique is now accepted as a standard treatment for EGC. In fact, the Japanese government recently approved insurance coverage for ESD treatment costs at twice the rate for conventional EMR, primarily because of its demonstrated effectiveness in the en bloc removal of large EGCs.

ESD is associated with significant drawbacks, however, including longer procedure times and a higher risk of complications. It also requires extensive training, so a standardized ESD training program is needed to ensure its successful dissemination in the future.

## Clinical Outcomes of Endoscopic Resection for EGC

The clinical outcomes of EMR have been studied in such great detail that successful outcomes observed from these studies have allowed EMR to become the standard treatment for EGC in Japan. Kojima et al [10] reviewed the outcomes of EMR from 12 major Japanese institutions. The inject, lift and cut, EMR with a cap-fitted panendoscope (EMR-C), and EMR with ligatim (EMR-L) techniques were most commonly used and achieved en bloc resections in approximately three-quarters of all patients who underwent such techniques. The disease-specific survival rate was 99%, although not all studies reported long-term outcomes.

As previously indicated, however, standard EMR techniques are associated with a higher risk of recurrence, especially when resections are piecemeal or resection margins are not tumor free histologically. The risk of local recurrence after EMR varies from 2% to 35%. In some specialized centers in Japan, studies on the long-term outcomes of patients who have had endoscopic resections using the expanded criteria are currently under way. The incidence of metachronous multiple GC in patients who have undergone endoscopic resection on their first lesions also needs to be prospectively investigated to determine the appropriate interval for effective surveillance endoscopy.

## Future Prospects

The endoscopic resection technique has been demonstrated to be safe, effective, and applicable to a wide range of clinical situations. Rapid technological progress in combination with the development of ESD has been responsible for advances in the endoscopic resection of not only EGC but also esophageal and colorectal cancers [11].

Although several endoscopic devices have been developed to make ESD easier and safer, this technique still requires a highly experienced endoscopist because the procedure is performed using a single gastroscope, thus requiring one-handed surgery. More recently, procedures involving countertraction of lesions such as percutaneous traction-assisted EMR (PTA-EMR), magnetic-anchor-guided (MAG) ESD, and sinker-assisted ESD have been described in various published reports.

To further extend the indications for treating EGC with less-invasive surgery, endoscopic resection combined with laparoscopic regional LN dissection should be given