The Efficacy of Endoscopic Submucosal Dissection Compared with Modified Endoscopic Aspiration Mucosectomy by Assessing the Short-term Therapeutic Results for Differentiated Mucosal Gastric Cancer

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Abstract. *Background: We developed a modified method of endoscopic aspiration mucosectomy (m-EAM) which includes the pre-cutting of the peripheral mucosa before aspiration, and which has been employed in this department since 1998. An endoscopic submucosal dissection (ESD), which enables the resection of a larger area of the lesion using newly-developed surgical devices, has also been employed here since March 2003. This study was performed to investigate the efficacy of ESD at the present time by assessing the short-term therapeutic results for the procedure in patients with a preoperative diagnosis of early-stage differentiated gastric mucosal cancer, by tumor diameter, as well as by comparing these results with those obtained previously with m-EAM. Patients and Methods: The study included 110 patients with a preoperative diagnosis of early-stage differentiated gastric mucosal cancer (57 underwent m-EAM and 53 received ESD). A comparison was made between these two groups regarding the short-term therapeutic response (en bloc resection rate, curability, complications, and days of postoperative hospitalization) by the tumor diameter. Results: The en bloc resection rate was significantly higher for patients with a tumor measuring 21 mm or larger who underwent ESD in comparison to that for those with a similar tumor size who underwent m-EAM ($p<0.05$). Complications were reported significantly more frequently in patients treated with ESD for a tumor measuring 11 mm or larger ($p<0.05$) in comparison those treated with m-EAM. There was no significant difference between the two groups with regard to the curability and the days of postoperative hospitalization. Conclusion: This study confirmed the efficacy of the ESD procedure which enables surgeons to perform a more reliable en bloc tumor resection.*

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Endoscopic aspiration mucosectomy (EAM) for the treatment of early gastric cancer was developed by Torii *et al*. (1) in 1995. The procedure has, however, been associated with some difficulty in precisely targeting the lesion in the center of the resected field because the lesion is first aspirated by the hood attached to the endoscope and then resection is performed (2). In 1998, the authors developed a modified method of EAM (m-EAM), which includes an incision around the tumor before EAM to guide subsequent aspiration mucosectomy, and that method has been employed in this Department since that time (3). On the other hand, the usefulness of an endoscopic submucosal dissection (ESD), which enables the resection of a larger early gastric tumor using newly-developed devices such as an insulated-tipped diathermic knife, has been documented (4, 5). Therefore, this procedure has also been employed here since March 2003, in order to achieve more reliable results. However, a great deal of experience is required to master the ESD procedure, and there is a significant technical gap between respective medical centers as well as a difference in the level of difficulty depending on the tumor diameter. This study was performed to investigate the efficacy of ESD at the present time by assessing the short-term therapeutic results for the procedure in patients with a preoperative diagnosis of differentiated gastric mucosal cancer, by tumor diameter, as well as by comparing these results with those obtained previously with m-EAM.

Patients and Methods

Patients. The study included 110 patients with a preoperative diagnosis of differentiated gastric mucosal cancer who underwent endoscopic mucosal resection in this Department. These patients were divided according to the procedures performed: 57 underwent m-EAM from April 1998 to March 2003, and 53 received ESD from

April 2003 to March 2007. A comparison was made between these two groups regarding the following parameters.

Demographic characteristics: The patient demographic characteristics were examined for their sex ratio, mean age, tumor diameter, and histological depth of the lesions.

Short-term therapeutic response: Short-term therapeutic response was assessed by the tumor diameter (10 mm or smaller, 11 to 20 mm, or 21 mm or larger), regarding the *en bloc* resection rate, curability, concurrent diseases, and days of postoperative hospitalization. The curability of gastric cancer was determined based on the curative potential defined in the Japanese Classification of Gastric Carcinoma, 2nd English Edition (6) and its guidebook (7). Based on the histological findings, the curative potential was defined as follows: Resection EA: depth M (mucosa), histological papillary or tubular adenocarcinoma without ulceration or an ulcer scar, with tumor-free lateral (LM) and vertical (VM) margins, and no lymphatic or venous invasion; resection EB: no marginal involvement, but failing to satisfy the other criteria for resection EA; resection EC: involvement of the LM and/or VM (6, 7). If the patient developed a perforation as indicated by the presence of free air, or a hemorrhage associated with a decrease in hemoglobin level of 2 g/dl or more or requiring endoscopic hemostasis during the study, then these events were considered to be complications of this procedure.

Statistical analysis. A statistical analysis was performed using the chi-squared test, the Mann-Whitney *U*-test, and *t*-test. A *p*-value less than 0.05 was considered to be statistically significant.

Results

Demographic characteristics. In the m-EAM group, there were 46 males and 11 females, with a mean age of 70.1 years, ranging from 50 to 88 years. The mean tumor diameter was 14.5 mm, ranging from 3 to 40 mm. The histological depth of the lesion was mucosal/submucosal (M/SM) 54/3. On the other hand, there were 35 males and 18 females in the ESD group, with a mean age of 72.3 years, ranging from 54 to 89 years. The mean tumor diameter was 18.9 mm, ranging from 4 to 60 mm, and the histological depth of the lesion was M/SM 44/9, both of which indicated a significantly larger tumor size in the ESD group than in the m-EAM group ($p<0.05$).

Short-term therapeutic response.

En bloc *resection rate:* In the m-EAM group, the en bloc resection rate was 86.2%, 61.1% and 10.0% for patients with a tumor size of 10 mm or smaller, 11 to 20 mm, and 21 mm or larger, respectively, while in the ESD group it was 92.3%, 81.8% and 88.2%, respectively. The rate was significantly higher for patients with a tumor measuring 21 mm or larger undergoing ESD in comparison to that for those with a similar tumor size undergoing m-EAM ($p<0.05$).

Curability: The curability as expressed in EA/EB/EC, was 23/4/2, 10/8/0 and 2/6/2 for patients in the m-EAM group with a tumor size of 10 mm or smaller, 11 to 20 mm, and 21 mm or larger, respectively, while in the ESD group it was 9/4/0, 14/9/1 and 9/5/3, respectively.

In patients with histologically documented gastric mucosal cancer, the EA/EB/EC was 23/4/1, 10/7/0 and 2/6/1 for patients in the m-EAM group with a tumor size of 10 mm or smaller, 11 to 20 mm, and 21 mm or larger, respectively, while in the ESD group it was 9/2/0, 13/5/0, and 9/4/2, respectively, thus indicating no significant difference between the two groups.

Complications of the procedure. In the m-EAM group, a perforation was noted in 2, 0 and 0 patients, and a hemorrhage was noted in 1, 2, and 0 patients with a tumor size of 10 mm or smaller, 11 to 20 mm and 21 mm or larger, respectively, while in the ESD group, 1, 6, and 6 patients, and 0, 0 and 2 patients experienced these complications, respectively. These complications were reported significantly more frequently in patients with a tumor measuring 11 mm or larger undergoing ESD($p<0.05$) in comparison to those undergoing m-EAM.

Days of postoperative hospitalization. In the m-EAM group, the days of postoperative hospitalization were 7.3, 8.6 and 9.2 in patients with a tumor size of 10 mm or smaller, 11 to 20 mm, and 21 mm or larger, respectively, while in the ESD group they were 6.1, 7.2, and 8.4, respectively, thus indicating no significant difference between the two groups.

Discussion

ESD is a procedure which involves the endoscopic detachment of the submucosal layer followed by the resection of the lesion together with the gastric mucosa. This procedure has been increasingly performed in patients with early gastric cancer since the development of the insulated-tipped diathermic knife (4). It has been documented that no lymph node metastasis is noted in patients with gastric cancer, especially differentiated gastric mucosal cancer, even in cases with a tumor size exceeding 2 cm (9), which is the basic criteria defined in the Gastric Cancer Treatment Guidelines (8) for determining whether ESD can be performed for a relevant case. Therefore, this procedure enables the en bloc resection of such larger lesions and is thus expected to be indicated for a broader range of gastric cancer cases (10-13). On the other hand, resection of a tumor specimen measuring 25 mm or larger in size is easily achieved in patients who undergo a conventional EAM, including m-EAM (2, 14). Based on these observations, the current study compared the short-term therapeutic results for ESD, which has been performed in this Department since April 2003, with that for modified EAM, exploring the future potential of endoscopic mucosal resection (EMR) for early gastric cancer.

A comparison of patient demographic characteristics revealed the tumor diameter was significantly larger in the ESD group than in the m-EAM group. This was considered to be a

reflection of recent trends that a broader range of indications for EMR for early gastric cancer is accepted (9-13).

Therefore, the tumor diameter was matched between the ESD and m-EAM groups before the comparison of therapeutic response for these groups was made using the en bloc resection rate, curability, concurrent perforation or hemorrhage, and days of postoperative hospitalization.

Generally, EAM and other procedures which involve tumor aspiration have been associated with a lower en bloc resection rate in patients with tumors measuring 20 mm or larger (15), and the rate is approximately 50% for tumors exceeding 16 mm in diameter (16). In contrast, the en bloc resection rate for ESD is independent of the tumor diameter (12, 13, 17), and some studies show a favorable resection rate of 95% or higher (12). In the present study, the en bloc resection rate decreased as the tumor diameter increased in the m-EAM group, while in the ESD group the rate was almost constant for different tumor sizes. This finding was associated with a significantly higher en bloc resection rate for patients with a tumor measuring 21 mm or larger treated by ESD in comparison to those with the same tumor size treated by m-EAM.

No significant difference was noted in the curability between the ESD and m-EAM groups, and a similar result was observed even when the analysis was limited to patients with mucosal cancer. A high complete resection rate is obtained for both the aspiration procedure (16, 18) and ESD (10, 11, 17), with a favorable prognosis in the patients who achieve a complete resection (18, 19). However, the complete resection rate cannot be simply compared between these methods, since with the aspiration procedure a partial resection may be considered to be a complete resection if mucosal reconstruction is feasible, while such a case is not acceptable for the ESD procedure. In addition, there have been few studies assessing the results based on the curative potential defined in the Japanese Classification of Gastric Carcinoma (6, 7). In particular, the degree of cure defined as EB is ambiguous, and careful postoperative follow-up is necessary for both the ESD and aspiration cases if it is difficult to determine the cancer curability.

Both the ESD and m-EAM procedures involve peripheral mucosal cutting around the tumor, however, ESD requires a further detachment of the submucosal layer, which may be associated with a higher risk of intraoperative perforation or hemorrhage. In this study, complications, especially perforation, were more frequently noted during the ESD procedure in patients with tumors measuring 11 mm or greater in size. The incidence of such perforation concurrent with ESD is related to the performance level of the surgeon (20, 21), and one of the major issues relevant to this issue is that of blind procedures carried out by an experienced surgeon (21). On the other hand, the incidence of intraoperative hemorrhage was relatively low in both the ESD and m-EAM groups, which was partly attributable to the criteria for such a hemorrhage set in this study at 2 g/dl or greater decrease in the hemoglobin level or hemorrhage requiring endoscopic hemostasis procedures. Careful hemostasis after a tumor resection is definitely necessary to prevent intraoperative hemorrhaging.

The length of postoperative hospitalization was successfully reduced using a clinical path for the perioperative management of patients (22). However, in patients developing intraoperative complications including perforations, the number of hospital days may be prolonged with a delay of the start of oral nutrition intake (23). In this study, no significant difference was noted in the postoperative hospitalization days in patients with more intraoperative complications between the ESD and m-EAM groups. Perforations occurring during the ESD procedure have been associated with a smaller hole size than with other procedures; therefore, no major consequences are expected regarding the patient's postoperative condition if the perforated area can be properly closed during surgery.

The results of this study showed that the short-term therapeutic results in terms of curability and the length of postoperative hospitalization were similar between the ESD and m-EAM procedures. In addition, the en bloc resection rate was higher in patients receiving ESD although these patients more frequently reported intraoperative complications. However, the incidence of such complications can be reduced with improvements in both the surgical techniques and the proficiency of the surgical procedures. This study confirmed the efficacy of the ESD and shows it allows surgeons to perform a more reliable en bloc tumor resection.

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