Perioperative Complications of Endoscopic Submucosal Dissection for Early Gastric Cancer in Elderly Japanese Patients 75 Years of Age or Older

Daisuke Chinda, Yoshio Sasaki, Tetsuya Tatsuta, Kiyoto Tsushima, Toyohito Wada, Tadashi Shimoyama and Shinsaku Fukuda

Abstract

Objective The number of endoscopic submucosal dissection (ESD) procedures for early gastric cancers among patients 75 years of age or older has been increasing. We herein examined both the outcomes and complications of ESD in elderly patients.

Methods We investigated the effects of underlying diseases, lesion characteristics, treatment outcomes and complications during and in the postoperative periods of ESD among elderly patients 75 years of age or older versus non-elderly patients less than 75 years of age.

Patients A total of 318 early gastric cancers in consecutive 307 patients, all of whom underwent ESD for gastric cancer, were included in this study.

Results The number of patients with hypertension and ischemic heart disease was significantly higher in the elderly group than in the non-elderly group. The proportion of lesions with an absolute indication, extended indication or no indication was not significantly different between the groups. During the ESD procedure, the use of atropine sulfate for bradycardia was significantly more frequent in the elderly group. No significant differences were observed between the groups in terms of the treatment for hypertension, oxygen administration or incidence of perforation. In addition, there were no significant differences with respect to oxygen administration, postoperative bleeding or the occurrence of fever and/or pneumonia after the ESD procedure.

Conclusion Although bradycardia was more frequently observed in the elderly patients during ESD in this study, ESD was performed safely and managed appropriately, with infrequent postoperative complications. ESD appears to be effective, even in elderly patients.

Key words: ESD procedure, elderly patients, perioperative complications, lesion characteristics, treatment outcomes

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Introduction

Endoscopic submucosal dissection (ESD) is now widely used for the treatment of early gastric gastrointestinal neoplasms (1). In comparison with conventional endoscopic mucosal resection, ESD can be used to achieve a higher rate of en-bloc resection as well as an accurate pathological diagnosis (2). However, ESD has a number of disadvantages, including the need for a high level of technical skill, a long operative time and a high frequency of complications (3-5). Therefore, reducing body movements with sedation is important for performing a safe and successful ESD procedure (6).

The increase in the elderly population in Japan has led to an increase in the number of gastric cancer-related deaths,
principally because this malignancy is more common in patients 80 years of age or older (7). Furthermore, in Japan, it is expected that the incidence of gastric cancers in the elderly will increase further in the near future, as the prevalence of Helicobacter pylori infection is high in populations 60 to 80 years of age. Therefore, the number of patients who require ESD for gastric cancer is expected to increase among elderly patients (i.e. 75 years or older). Furthermore, the incidence of systemic disease increases with increasing age. Although many studies have assessed perioperative complications related to the general ESD procedure (8, 9), only a few studies have examined the safety of the procedure with respect to the perioperative period in patients 75 years of age or older. A number of recent reports have also described the results of ESD used to treat gastric cancers in elderly patients; however, there is still no clear consensus regarding the outcomes and associated complications of this procedure (10-13). It is noteworthy though that a Japanese multicenter study demonstrated that curative ESD may contribute to improving survival, even in patients 80 years of age or older (7).

This study was performed in order to investigate the effects of underlying diseases on complications arising from ESD used to treat gastric cancer and evaluate the management protocol for these complications during both the procedure itself and in the perioperative period in elderly patients versus non-elderly patients.

<table>
<thead>
<tr>
<th>Table 1. Patients’ Characteristics in the Elderly and Non-elderly Groups</th>
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<tr>
<td>Mean age (SD)</td>
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<tr>
<td>Gender ratio (M:F)</td>
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<tr>
<td>Hypertension</td>
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<tr>
<td>Hyperlipidemia</td>
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<tr>
<td>Diabetes</td>
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<td>Ischemic heart disease</td>
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<td>Arrhythmia</td>
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<td>Cerebral infarction</td>
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<td>Liver cirrhosis</td>
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<td>Chronic renal failure</td>
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<td>History of abdominal surgery</td>
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<td>Antithrombotic therapy</td>
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**Materials and Methods**

**Patients**

A total of 318 early gastric cancers in consecutive 307 patients, all of whom underwent ESD for gastric cancer at Aomori City Hospital between April 2004 and March 2009, were included in this study. Patients were considered to be indicated for ESD if they decided to undergo the procedure after being informed of the state of their diseases as well as the complications and perioperative risks of ESD, regardless of age. In Japan, an age 75 years old or older is defined as ‘old-old,’ and a new health insurance system for the super aged society was established in April 2008 (14). Therefore, in this study, patients 65-74 years of age were classified as ‘young-old’ and those 75 years of age or older were classified as ‘old-old.’ We subsequently compared the differences between the elderly group (109 lesions in 102 patients) and the non-elderly group (209 lesions in 205 patients).

In comparison to the ‘young-old’ patients, ‘old-old’ patients more often have multiple diseases and functional disorders that influence their activities of daily living (11, 14, 15). The underlying diseases in each group are shown in Table 1. The patients were defined as having hyperlipidemia, diabetes, ischemic heart disease, arrhythmia, cerebral infarction, liver cirrhosis or chronic renal failure if any of these conditions had been previously diagnosed and were currently being treated. The proportion of patients with hypertension, diabetes, ischemic heart disease and liver cirrhosis was significantly higher in the elderly group than in the non-elderly group. Furthermore, the proportion of patients taking antithrombotic therapy was significantly higher in the elderly group. There were no significant differences in the incidence of any of the other underlying diseases or a history of previous abdominal surgery.

**ESD procedure**

ESD was performed using a conventional single channel endoscope (GIF-H260, Olympus, Tokyo, Japan) with a hood, and an ERCP cannula was fixed to the outside of the scope for the water supply. The ESD procedure was primarily performed using the Needle Knife (KD-1L-1, Olympus), Hook Knife (KD-620LR, Olympus) and Flex Knife (KD-630L, Olympus) before June 2006. After this date, we primarily used a water jet short needle knife (Flush Knife; DK 2618JN15, DK2618JB15, Fujinon, Tokyo, Japan). We also used a high-frequency generator with an automatically controlled system, ICC200 before September 2007 and VIO300D thereafter (both supplied by ERBE, Tübingen, Germany). The VIO300D was connected with the water jet pump used in the Flush Knife.

We administered an antibiotic (cefotiam 2.0 g/day) for three days from after the day of surgery. A repeat endoscopic examination was performed two days after ESD, and meals were restarted the third day after ESD. There were no significant differences between the two groups with respect to the hospitalization period (overall mean stay: 9.6 days).

**Statistical analysis**

Student’s t-test, Fischer’s exact probability test and the Mann-Whitney U-test were used to examine differences between the elderly and non-elderly groups. The differences were considered to be statistically significant at a p value of <0.05.
order to treat bradycardia during ESD, we administered atro-
tients and 47.8% of the non-elderly patients. None of the
hydrochloride was administered in 43.1% of the elderly pa-
systolic arterial pressure exceeded 160 mmHg. In order to
procedure. We administered nicardipine hydrochloride if the
antispasmodic agents. Scopolamine butylbromide or glucagon were also used as
patients in the elderly and non-elderly groups, respectively.

Sedation is commonly used to relieve anxiety and dimin-
without ulceration. Lesions classified as an extended in-
notation met the following criterias: i) differentiated mucosal
adenocarcinoma without ulceration larger than 20 mm in di-
ameter, ii) differentiated mucosal adenocarcinoma with ul-
ceration less than or equal to 30 mm in diameter, iii) differ-
etiated mucosal adenocarcinoma with minimal submucosal
invasion of 500 μm or less and a diameter no greater than
30 mm, iv) undifferentiated mucosal adenocarcinoma with-
out ulceration and measuring less than 20 mm in diameter
(16-19). As shown in Table 2, the proportions of lesions
with an absolute indication, extended indication and no-
indication were not significantly different between the
groups. Similarly, there were no significant differences in
the mean operative time, en-bloc resection rate or complete
resection rate between the groups.

Management during the ESD procedure

Sedation is commonly used to relieve anxiety and dimin-

in only one case in the non-elderly group. Postoperative perforation occurred in only
one case in the non-elderly group. The diagnosis of perfora-
tion, as evidenced by Salem (2015) and others, is the detection of mesenteric fat on endoscopy or free air on radiography or computed tomography (CT). There were no significant differences in the incidence of perforation between the elderly (2.0%) and the non-elderly (2.9%) groups. Even when perforation occurred, we were able to successfully treat it with clipping, and the ESD procedure was completed in all eight cases.

Complications after ESD

The details of the complications observed after ESD are shown in Table 4. There were not significant differences between the two groups with respect to the need for oxygen administration (after the end of ESD and until the next morning) or incidence of fever (38°C or higher) or pneumonia (as diagnosed on radiography or CT the following day). No patients exhibited leg edema or dyspnea, symptoms suggestive of deep vein thrombosis. Postoperative bleeding was defined as a decrease in the hemoglobin level by more than 2.0 g/dL on the day after the operation or the second occurrence of bleeding more than two days after ESD. Postoperative bleeding occurred in 5.9% and 4.9% of the patients in the elderly and the non-elderly groups, respectively (NS). Second-look endoscopy was performed on the second day after ESD, with endoscopic hemostasis treatment (including a preventive mark) if necessary. There were no significant differences in the number of patients requiring endoscopic hemostasis treatment between the elderly (16.7%) and non-elderly (19.7%) groups. Postoperative perforation occurred in only one case in the non-elderly group.

Discussion

The prevalence of cardiovascular diseases and proportion of patients receiving antithrombotic therapy were significantly higher and the mean tumor size and resected specimens were significantly larger in the elderly than in the non-elderly groups. In addition, the rate of en-bloc resection rate was 95% or more in both groups, while the rate of complete resection was 87.2% in the elderly group versus 79.9% in the non-elderly group. These findings indicate that ESD for early gastric cancer is both effective and safe in elderly as well as non-elderly patients.

In all patients, we initially used pethidine hydrochloride (35 mg/body), together with midazolam if appropriate, although caution is required when administering the latter, as its use in the elderly often causes a decrease in the oxygen

<table>
<thead>
<tr>
<th>Table 2. Categories of Lesions and Treatment Outcomes</th>
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<tbody>
<tr>
<td>Elderly group</td>
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<tr>
<td>Indication lesion</td>
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<tr>
<td>Extended indication lesion</td>
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<tr>
<td>No-indication lesion</td>
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<tr>
<td>Mean tumor size (mm)</td>
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<tr>
<td>Mean operated specimen size (mm)</td>
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<tr>
<td>Mean operative time (min)</td>
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<tr>
<td>En-bloc resection rate (%)</td>
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<td>Complete resection rate (%)</td>
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</table>

Results

Characteristics and categories of lesions and treatment outcomes

The macroscopic type of gastric cancer was classified according to the guidelines of the Japanese Gastric Center Association. The lesions were considered an absolute indication for ESD if they consisted of a differentiated mucosal adenocarcinoma measuring no greater than 20 mm in diameter without ulceration. Lesions classified as an extended indication met the following criteria: i) differentiated mucosal adenocarcinoma without ulceration larger than 20 mm in diameter, ii) differentiated mucosal adenocarcinoma with ulceration less than or equal to 30 mm in diameter, iii) differentiated mucosal adenocarcinoma with minimal submucosal invasion of 500 μm or less and a diameter no greater than 30 mm, iv) undifferentiated mucosal adenocarcinoma without ulceration and measuring less than 20 mm in diameter (16-19). As shown in Table 2, the proportions of lesions with an absolute indication, extended indication and no-indication were not significantly different between the groups. Similarly, there were no significant differences in the mean operative time, en-bloc resection rate or complete resection rate between the groups.

Characteristics and categories of lesions and treatment outcomes

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Management during the ESD procedure

Sedation is commonly used to relieve anxiety and diminish pain, discomfort and memories of the procedure (6). In order to achieve these goals, we used pethidine hydrochloride, followed by midazolam when appropriate. Midazolam was required for proper sedation in 56.6% and 62.7% of the patients in the elderly and non-elderly groups, respectively. Scopolamine butylbromide or glucagon were also used as antispasmodic agents.

Table 3 shows the complications observed during the ESD procedure. We administered nicardipine hydrochloride if the systolic arterial pressure exceeded 160 mmHg. In order to treat hypertension during the ESD procedure, nicardipine hydrochloride was administered in 43.1% of the elderly patients and 47.8% of the non-elderly patients. None of the patients required medications for reduced blood pressure. In order to treat bradycardia during ESD, we administered atro-
blood pressure during the ESD procedure. This may be because is difficult to control bleeding when the blood pressure is elevated. In particular, controlling systolic blood pressure after ESD is also important for preventing post-ESD bleeding (22). In the current study, the proportion of patients with hypertension was significantly higher in the elderly group before ESD. Therefore, hypertension should be treated in elderly patients in order to prevent bleeding and reduce the risk of cerebrovascular and cardiovascular disorders associated with a continuously high blood pressure. In our study, however, the diagnosis and treatment of hypertension was not associated with the detection of a high blood pressure during the ESD procedure. This may be because the hypertensive patients took their medications on the morning of the day of surgery. In addition, the development of high blood pressure during ESD depends on other factors, such as pain, rather than the underlying diseases itself.

According to the modified Vasovagal Syncope International Study (VASIS), the hemodynamic responses of vasovagal syncope can be classified into three types, and one standard for diagnosing bradycardia is the detection of a pulse less than 40 beats per minute (bpm) (23, 24). The onset of bradycardia during ESD is often related to the vagal reflex caused by an excess of air and/or difficulty in inserting the endoscope. Although such bradycardia is usually improved by addressing these factors, the administration of atropine sulfate is sometimes necessary. Therefore, in this study, ‘bradycardia’ during ESD was defined as a heart rate less than 40 bpm in patients administered atropine sulfate. Bradycardia occurred more frequently during the operation among the elderly patients, although this finding did not have a significant influence on the treatment outcome.

Perforations occurred during ESD in two elderly patients and six non-elderly patients. In most previous cases, perforation was treated conservatively (8, 11). Similarly, in our cases, we were able to complete ESD in such cases, and all eight patients were successfully treated conservatively. Several reports have indicated that risk factors for perforation include tumor location (upper stomach), tumor diameter (> 20 mm), massive submucosal invasion, hypertension and the level of experience of the endoscopists (8, 11). Of the two elderly patients in whom perforation occurred in this study, one had a tumor measuring 80 mm in diameter, while the other, who had no other apparent risk factors, was treated by an endoscopist with insufficient experience.

When performing endoscopic procedures in antithrombotic users, physicians must consider the risk of bleeding and/or thrombosis associated with stopping various medications (25, 26). For example, it is known that the onset of cardiovascular events or cerebral infarction increases approximately three times by stopping antplatelet therapy (27, 28), and the development of serious thromboembolism following the discontinuation of anticoagulant therapy has been reported in several conditions (29-31). A recent report showed that significant risk factors for delayed bleeding include a reduced platelet count, extended prothrombin time, large extent of resection and positive/in-determinate lateral margin (32). Another report showed that a significantly higher proportion of elderly patients receive

<table>
<thead>
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<th>Table 3. The Complications Observed During the ESD Procedure</th>
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<tbody>
<tr>
<td>Elderly group</td>
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<tr>
<td>---------------</td>
</tr>
<tr>
<td>Increase in blood pressure (&gt;160 mmHg)</td>
</tr>
<tr>
<td>Decrease in blood pressure (&lt;70 mmHg)</td>
</tr>
<tr>
<td>Bradycardia (&lt;40 beats per minute)</td>
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<tr>
<td>Decrease in oxygen concentration (Sat O2&lt;90%)</td>
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<tr>
<td>Severe bleeding</td>
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<tr>
<td>Perforation</td>
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Table 4. The Complications Observed after the ESD Procedure

<table>
<thead>
<tr>
<th>Elderly group</th>
<th>Non-elderly group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen administration</td>
<td>31 (30.4%)</td>
<td>60 (29.3%)</td>
</tr>
<tr>
<td>Fever</td>
<td>2 (2.0%)</td>
<td>3 (1.5%)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0 (0%)</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Postoperative bleeding</td>
<td>6 (5.9%)</td>
<td>10 (4.9%)</td>
</tr>
<tr>
<td>Endoscopic hemostasis</td>
<td>17 (16.7%)</td>
<td>39 (19.7%)</td>
</tr>
<tr>
<td>(including prevention)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postoperative perforation</td>
<td>0 (0%)</td>
<td>1 (0.5%)</td>
</tr>
</tbody>
</table>
anticoagulant drugs compared to other patients and that these individuals are at an increased risk of postoperative bleeding (33). In July 2012, the Japan Gastroenterological Endoscopy Society (JGES) published guidelines for the use of endoscopic procedures in antithrombotic drug-users, stating that antithrombotic therapy should be continued prior to ESD (34). However, in this study, antithrombotic therapy was discontinued according to the recommended cessation period (35) because the patients received ESD before the JGES guidelines were announced. Various endoscopic hemostasis methods have been established (3, 4), and a retrospective study recently reported that the application of preventive coagulation of visible vessels in the area of resection after ESD may result in a lower rate of bleeding (36). In the current study, the incidence of postoperative bleeding was not significantly different between the elderly and the non-elderly groups, although the elderly patients more frequently required antithrombotic therapy. Our findings suggest that the use of a suitable washout period for antithrombotic drugs and preventive endoscopic hemostasis may reduce the risk of postoperative bleeding, even among elderly patients using antithrombotics.

Although elderly patients more frequently have underlying diseases versus non-elderly patients, our results showed no significant differences between the two groups in the incidence of perioperative complications, except for intraoperative bradycardia. ESD was performed safely and managed appropriately, with infrequent postoperative complications, although bradycardia was more often detected in the elderly patients. In conclusion, ESD for early gastric cancer appears to be safe and effective, even in elderly patients. ESD should be considered in patients who understand the risks and benefits of the procedure, even those 75 years of age or older.

The authors state that they have no Conflict of Interest (COI).

References


