Impact of gastric endoscopic submucosal dissection in elderly patients

The latest single center large cohort study with a review of the literature

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1. Introduction

According to the Japanese Ministry of Health, Labour and Welfare in 2015, the number of individuals aged over 65 years is expected to reach 36.57 million and reach a peak in 2042, at 38.78 million individuals. The proportion of elderly individuals aged over 75 years in the entire population is expected to exceed 25% by 2055\textsuperscript{[11]} Furthermore, the increased number of elderly in society has led to an increase in the occurrence of various underlying diseases as well as the rate of oral antithrombotic therapy\textsuperscript{[12]}

Nowadays, endoscopic submucosal dissection (ESD) has become a useful minimally invasive treatment for elderly patients with early-stage gastric cancer\textsuperscript{[3–5]} because it is less invasive than open surgical procedures and is highly advantageous in terms of organ preservation\textsuperscript{[6–7]}. Recently, some patients in the expanded indications group, that is, very elderly patients (age over 80 years) who are taking anticoagulation drug, are treated by ESD. However, there are few discussions on this topic, such as the occurrence of procedure-related adverse events when performing ESD in elderly patients\textsuperscript{[8–11]}

In the present study, we retrospectively evaluated the therapeutic outcomes of ESD for elderly patients to clarify their benefit and harm.

2. Patients and methods

2.1. Patients

Among 501 lesions from 452 patients (mean age: 71.9±9.5 years; male-to-female ratio: 328:124) who underwent ESD at our hospital between November 2012 and November 2016, those
aged over 80 years constituted group A (107 lesions among 94 patients with a mean age of 83.9 ± 3.9 years and a male-to-female ratio of 65/29), those aged 65 to 79 years constituted group B (293 lesions among 266 patients with a mean age of 72.3 ± 4.2 years and a male-to-female ratio of 190/76), and those aged less than 65 years constituted group C (101 lesions among 92 patients with a mean age of 58.1 ± 6.2 years and a male-to-female ratio of 73/19).

When one of the conditions in the absolute and expanded indications for curative resection is not met, it is defined as noncurative resection.

A proton pump inhibitor was administered to all patients on the day of ESD, and use was regularly continued for at least 36 days after ESD. Second-look endoscopy was not performed after ESD without post-ESD bleeding. Antithrombotic drug treatment was managed according to the JGES guidelines in 2014.[13]

3. Results

Upon comparing groups A, B, and C, the prevalence of underlying diseases, including heart disease, lung disease, kidney disease, and cerebrovascular disease, were 41.5% (39/94), 28.2% (39/94), and 9.8% (9/92), respectively, indicating a significantly higher prevalence in groups A and B than in group C. The rates of administering oral antithrombotic therapy were 33.0% (31/94), 22.2% (59/266), and 6.5% (6/92) in groups A, B, and C, respectively, and this rate was found to significantly increase with age (Table 1).

### 2.2. ESD procedure

The GIF-Q260J (Olympus Medical Systems Corp, Tokyo, Japan) endoscope was primarily used. Devices used included the insulation-tipped diathermic knife (IT knife) 2 (Olympus Medical Systems Corp, Tokyo, Japan) and dual knife (Olympus Medical Systems Corp.). Totally, 20 mL of physiological saline with 0.8 mg of indigo carmine was used as the local injection solution.

The indications for endoscopic resection and postendoscopic resection evaluation were determined in accordance with the Japanese Classification of Gastric Carcinoma in 2016 (ver. 3).[12] Lesions that met absolute indications were defined as differentiated cancer diagnosed as macroscopic intramucosal carcinoma (cT1a) measuring less than 2 cm and lesions limited to UL (−), regardless of the macroscopic type. Lesions that met expanded indications were defined as

- UL (−) cT1a differentiated carcinomas greater than 2 cm in diameter,
- UL (+) cT1a differentiated carcinomas less than 3 cm in diameter, and
- UL (−) cT1a undifferentiated carcinomas less than 2 cm in diameter.

Lesions exceeding the expanded indication were considered as those that did not meet the inclusion criteria for endoscopic treatment. Furthermore, curative resection was determined based on all the following criteria being met: the tumor is resected en bloc, is < 2 cm in diameter, and is a differentiated type of cancer with a depth of pT1a, HM0, VM0, Lym (−), and v (−). Curative resection for lesions that met the expanded indications is determined when the tumor is resected en bloc and the resected specimen is

1. UL (−) pT1a differentiated carcinoma of ≥ 2 cm,
2. UL (+) pT1a differentiated carcinoma of < 3 cm,
3. UL (−) pT1a undifferentiated carcinoma of < 2 cm, or
4. differentiated-type with pT1b (SM1) invasion (less than 500 μm from the muscularis mucosae) of < 3 cm and HM0, VM0, Lym (−), and v (−).

### 2.3. Statistical analysis

The present study was performed with the approval of the Ethical Review Board of Tokyo Medical University Hospital (No. 2017-045). The 3 groups were compared in terms of the underlying disease, the presence or absence of oral antithrombotic therapy, therapeutic outcomes, the presence or absence of procedural accidents, and the treatment plan following noncurative resection. SPSS (version 22, Chicago, IL) was used for all statistical analyses. Analysis was performed using analysis of variance, and P < .05 was considered to indicate a significant difference.

### 3.1. ESD treatment outcomes

There were 73, 236, and 83 lesions corresponding to the indications in the guidelines; 27, 51, and 14 lesions that met the expanded indications, and 7, 6, and 4 lesions in groups A, B, and C, respectively, that did not meet the inclusion criteria for ESD. On comparing the pathological diagnosis of the resected specimens in each of the 3 groups in terms of differentiation, depth, presence or absence of ulceration, lymphatic invasion, and vascular invasion, no significant difference was observed (Table 2) (Fig. 1).

On comparing groups A, B, and C, there was no significant difference observed in the en bloc resection rate (96.3%...
| Categories of lesion. | >80 yr old | 65–79 yr old | <65 yr old | P-value |
|----------------------|-----------|-------------|-----------|--------|
|                       | Group A   | Group B     | Group C   |        |
| N (lesions)           | 107       | 293         | 101       |        |
| Location, U/M/L       | 22/24/61  | 52/82/159   | 15/27/59  |        |
| Tumor size, mm        | 17.5±14.2 | 15.6±9.6    | 13.1±8.2  |        |
| Absolute indication   | 68.2% (73/107) | 80.5% (236/293) | 82.2% (83/101) | .128   |
| Expanded indication    | 25.2% (27/107)  | 17.4% (51/293) | 13.9% (14/101) | .132   |
| Contraindication      | 6.5% (7/107)   | 2.0% (6/293) | 4.0% (4/101) | .925   |
| Histological type     | 95.3% (102/107) | 95.9% (281/293) | 95.0% (96/101) | .925   |
| Predominantly diff.    | 4.7% (5/107)    | 4.1% (12/293) | 5.0% (5/101) | .223   |
| Predominantly undiff.  | 95.3% (102/107) | 95.9% (281/293) | 95.0% (96/101) | .925   |
| Ulcer                 | 8.9% (9/94)     | 9.9% (20/266) | 5.0% (5/92)  | .325   |
| Palpation             | 95.8% (102/107) | 95.9% (281/293) | 95.0% (96/101) | .925   |
| Vascular involvement  | 8.4% (9/107)    | 6.5% (19/293) | 4.0% (4/101) | .925   |

| Group A: super elderly patients (>80 yr old), Group B: elderly patients (65–79 yr old), Group C: nonelderly patients 65 years. Location: L, lower stomach; M, middle stomach; U, upper stomach. Depth of invasion: M, mucosal cancer; SM1, tumor infiltration into the submucosal layer <500 µm from the muscularis mucosae; SM2, tumor infiltration into the submucosal layer >500 µm from the muscularis mucosae.

3.3. Noncurative cases

Among the patients in group A, the 19 cases with noncurative resections are presented in Table 6. Of these 19 patients, 3 patients underwent an additional surgical resection, 2 patients underwent additional endoscopic treatment by ESD or argon plasma coagulation, and 15 patients underwent follow-up observation. Follow-up observation at our hospital for noncurative resection cases involves examination for localized recurrence by endoscopy or CT at 6 months to 1 year following ESD. Five patients passed away while undergoing follow-up, including 3 patients who died from other causes after ESD; 1 patient who had multiple metastasis following ESD, and 1 patient who died due to poor nutritional status after additional surgery.

4. Discussion

Endoscopic mucosal resection was developed in the 1980s and led to the widespread popularity of endoscopic treatment for early-stage gastric cancer. 114 Subsequently, in the 1990s, the development of the IT knife and the advent of various devices led to the rapid popularization of ESD in Japan. 115, 116 Advantages of ESD include that it enables en bloc resection even of extensive lesions and accurate pathological evaluation. 117–123 Furthermore, the aging of the population is associated with an increased number of cases in which the selection of minimally invasive surgery is recommended for elderly patients from various perspectives, including postoperative quality of life (QOL) and procedural accidents. 22–23 Compared to open surgical procedures, ESD is minimally invasive, and has thus been established at various institutions as a highly effective endoscopic treatment for elderly patients. Reports of ESD in elderly patients are associated with various controversies, and many points remain unclear regarding safety, postoperative ADL (activities of daily life), and the approach for lesions that do not meet the inclusion criteria. In the present study, we analyzed the characteristics of the
Table 3

Treatment outcomes.

|                      | >80 yr old | 65–79 yr old | <65 yr old | P-value  |
|----------------------|------------|--------------|------------|----------|
| N (patients/lesions) | 94/107     | 266/293      | 92/101     |          |
| Complete en bloc resection rate | 91.6% (98/107) | 93.5% (274/293) | 94.1% (95/101) | P = .741 |
| Curative resection for absolute indication | 58.9% (63/107) | 57.7% (169/293) | 73.3% (74/101) |          |
| Curative resection for expanded indication | 23.4% (25/107) | 26.6% (78/293) | 15.8% (16/101) |          |
| Noncurative resection | 17.8% (19/107) | 15.7% (47/293) | 11.0% (11/101) |          |
| Curative resection for absolute and expanded indication | 82.2% (88/107) | 84.3% (246/293) | 89.1% (90/101) | P = .286 |
| Rate of additional operation for the noncurative resection | 15.8% (3/19) | 58.7% (27/46) | 63.6% (7/11) | P < .001 |
| Rate of complications | 9.6% (9/94) | 7.5% (20/266) | 4.3% (4/92) | P = .314 |
| Delayed bleeding | 6.4% (6/94) | 6.4% (17/266) | 4.3% (4/92) | P = .717 |
| Perforation | 3.2% (3/94) | 0.8% (2/268) | 0.0% (0/92) | P = .079 |
| Aspiration pneumonitis | 0.0% (0/94) | 0.4% (1/268) | 0.0% (0/92) | P = .706 |
| Operation time | 117.6 ± 92.5 | 103.8 ± 71.4 | 109.6 ± 63.7 | P = .346 |
| Days of hospitalization | 8.4 ± 5.3 | 8.0 ± 2.9 | 7.2 ± 1.6 | P = .001 |

Group A: super elderly patients (>80 yr old), Group B: elderly patients (65–79 yr old), Group C: nonelderly patients 65 years.

Figure 1. A 91-year-old man presenting a O-IIa lesion measuring 25 mm in the posterior wall of the upper gastric body, with por2 > sig (preoperative biopsy). Although the lesion did not meet the inclusion criteria, en bloc resection was performed by ESD as per the wishes of the patient’s family. Pathological findings included por2 > sig, O-IIa, 18 × 18 mm, pT1b2 (SM2 ≥800 μm), UL (−), ly (+), v (+), HM0, and VM1. The procedure was deemed a noncurative resection. Upon performing additional surgery, the subject developed postgastrectomy syndrome 1 month after surgery, which led to the gradual deterioration of his nutritional status due to impaired food intake. Seven months after surgery, the subject went into septic shock caused by a urinary tract infection and passed away. ESD = endoscopic submucosal dissection.
Patients receiving oral antithrombotic therapy are considered to be at high risk of developing thrombosis upon drug cessation; thus, heparinization was administered in accordance with the guidelines. However, in recent years, the risk of hemorrhage in heparinization has gradually become clear. Furthermore, disadvantages arise in routine clinical practice (eg, complications at hospital admission, and longer hospital stays). With the increased incidence of underlying diseases, there are many elderly patients who undergo oral antithrombotic therapy for the prevention of cerebrovascular and cardiovascular disease. In addition to the increased risk of late bleeding, since there is a negative medical economic effect (eg, the length of the hospital stay and cost of medical care), we believe that the continuation of antithrombotic therapy and the need for heparinization should be examined from various perspectives.

Group A included some patients for whom ESD was selected as minimally invasive treatment rather than open surgery for lesions that do not meet the inclusion criteria, as well as some patients who underwent follow-up observation without additional surgery for noncurative resection. In the present study, while the safety of ESD was suggested, a few procedural events occurred, including bleeding and perforation.

Until January 2018, the ESD study that compared with an elderly person and the nonelderly person was 11 cases in total (Table 7). Those studies reported the en bloc resection rates and complication. Most of these studies describe that there is not significant difference in en bloc resection rate and complication between the 2 groups similar to the present study.

Among limitations, in elderly patients, some procedures become fatal because the patients have considerably reduced residual function of various organs. Thus, more careful consideration for the treatment and management of the patient’s general condition is required. It has been reported that additional surgery for noncurative resection can help to improve the survival rate. However, as seen in the case presented above, there are some patients who undergo an additional resection for noncurative lesions by ESD, which consequently leads to the deterioration of their nutritional status due to impaired food intake caused by postgastrectomy syndrome; therefore, in cases of elderly patients, judgment can be difficult. While ESD is advantageous since it enables the removal of cancer, the burden of minimally invasive surgery cannot be ignored, and follow-up observation can also be considered an option. Additional surgery for elderly patients remains controversial and while there are no established clear determination criteria. Therefore, in addition to age, some experts consider that ADL, PS (performance status), and the prognostic nutritional index (Onodera’s PNI) could serve as factors to determine the treatment plan. Elderly patients are at high risk of dying from other diseases, and the treatment should be carefully determined, taking ADL and nutritional status into consideration. In the present study, on comparing the pathological diagnosis in terms of differentiation, depth, presence or absence of ulceration, lymphatic invasion, and vascular invasion, no significant difference was observed. On the other hand, there are reports that pathological risk factors are

| Table 4
| Characteristics of 96 patients receiving antithrombotic therapy. |
| --- |
| N | 96 |
| Age | 76.5±7.3 |
| Male/female | 73/23 |
| Comorbidity |
| Cerebral infarction | 30 (31.3%) |
| Ischemic heart disease | 43 (44.8%) |
| Atrial fibrillation | 18 (18.8%) |
| Internal carotid artery constriction | 6 (6.3%) |
| Deep-vein thrombosis | 3 (3.1%) |
| Arteriosclerosis obliterans | 2 (2.1%) |
| Antithrombotic agents |
| Aspirin | 50 (52.1%) |
| Thienopyridine | 24 (25.0%) |
| Clopidogrel | 13 (13.5%) |
| Other antithrombotic drugs | 13 (13.5%) |
| Warfarin | 11 (11.5%) |
| Novel oral anticoagulants (NOACs) | 9 (9.4%) |

### Table 5

| Treatment outcome of 96 patients receiving antithrombotic therapy. |
| --- |
| **Delayed bleeding** | **P_value** |
| Single antithrombotic versus | 5/73 (6.8%) versus |
| Multiple antithrombotics | 5/23 (21.7%) |
| No heparin bridging versus | 6/60 (7.5%) versus |
| Heparin bridging | 4/16 (25.0%) |
| **Heparin bridging** | **No heparin bridging** | **P_value** |
| N | 16/96 (16.7%) | 80/96 (83.3%) | P=.042 |
| Delayed bleeding | 4/16 (25.0%) | 6/60 (7.5%) | P=.036 |
| Days of hospitalization | 16.1±4.0 | 8.1±2.0 | P<.001 |
| Hospitalization request score | 62905±12348 | 48653±18136 | P=.003 |
Table 6  
Noncurative resection in over 80 yr patients.

| Case | Gender | Preoperated diagnosis  | Location | Histological type         | Size | Invasion | Age | ly | v | ul | Margin | resection | Additional treatment | Vital status | Cause of death in fatal cases | Follow up period |
|------|--------|------------------------|----------|---------------------------|------|----------|-----|----|---|----|--------|----------|------------------------|--------------|------------------------|-----------------|
| 1    | Male   | Expanded indication    | L        | por1>->tub2->tub1>->por2  | 42   | M        | 80  | +  | - | -  | Negative | En bloc resection | Follow up | Alive                  | 54 mo          |
| 2    | Male   | Contraindication lesion| U        | tub2->tub1->por2          | 27   | SM2      | 90  | -  | - | +  | Undear  | En bloc resection | Follow up | Alive                  | 50 mo          |
| 3    | Male   | Absolute indication    | L        | unclear                   | 10   | unclear  | 80  | -  | - | -  | Undear  | Pecemeal resection | ESD        | Alive                  | 45 mo          |
| 4    | Male   | Expanded indication    | M        | tub2>por                 | 15   | SM1      | 91  | +  | - | -  | Negative | En bloc resection | Follow up | Dead  Cerebral infarction | 13 mo          |
| 5    | Male   | Expanded indication    | U        | tub2->por2->tub1         | 45   | SM1      | 86  | -  | - | +  | Negative | En bloc resection | Follow up | Dead  Pneumonia         | 19 mo          |
| 6    | Male   | Contraindication lesion| M        | por1+sig>->tub2          | 15   | SM2      | 86  | +  | + | -  | Negative | En bloc resection | follow up | Dead  Untraceable      | 12 mo          |
| 7    | Female | Expanded indication    | L        | pap->tub1->tub2          | 58   | SM1      | 81  | +  | - | -  | Negative | En bloc resection | Surgery    | Alive                  | 31 mo          |
| 8    | Female | Absolute indication    | U        | tub1->tub2->pap          | 14   | M        | 83  | -  | - | -  | Positive | En bloc resection | Follow up | Alive                  | 25 mo          |
| 9    | Male   | Contraindication lesion| U        | sig->por2->tub2          | 25   | M        | 80  | -  | - | +  | Positive | En bloc resection | Follow up | Alive                  | 24 mo          |
| 10   | Male   | Contraindication lesion| U        | por2->sig                | 18   | SM2      | 91  | +  | + | -  | Positive | En bloc resection | Surgery    | Dead  Post operative nutritional disorder | 10 mo          |
| 11   | Male   | Contraindication lesion| U        | tub1->pap                | 65   | M        | 82  | -  | - | +  | Undear  | En bloc resection | Follow up | Alive                  | 21 mo          |
| 12   | Male   | Expanded indication    | U        | tub1                     | 34   | M        | 89  | -  | - | +  | Negative | En bloc resection | Follow up | Alive                  | 21 mo          |
| 13   | Male   | Expanded indication    | M        | tub2->tub1               | 20   | SM1      | 85  | -  | - | -  | Positive | En bloc resection | Follow up | Dead  Lumbar pressure fracture | 7 mo           |
| 14   | Male   | Expanded indication    | U        | tub2->tub1->por2         | 26   | SM2      | 80  | +  | + | +  | Positive | En bloc resection | Follow up | Alive                  | 16 mo          |
| 15   | Female | Absolute indication    | L        | por2->tub2               | 40   | SM2      | 91  | +  | + | -  | pPM pDM | No resection* | Surgery    | Dead  Metastasis (liver and lung) | 12 mo          |
| 16   | Male   | Absolute indication    | M        | unclear                  | 10   | unclear  | 83  | -  | - | -  | Negative | No resection* | APC       | Alive                  | 14 mo          |
| 17   | Male   | Expanded indication    | L        | tub1->tub2->tub1->pap    | 54   | SM1      | 84  | +  | - | -  | Negative | En bloc resection | Follow up | Alive                  | 7 mo           |
| 18   | Male   | Contraindication lesion| L        | tub1->tub2               | 11   | SM2      | 86  | +  | + | -  | Negative | En bloc resection | Follow up | Alive                  | 7 mo           |
| 19   | Male   | Absolute indication    | L        | tub1                     | 8    | M        | 87  | -  | - | -  | Undear  | En bloc resection | Follow up | Alive                  | 7 mo           |

*ly=lymph permeation, ul= ulcer, v= venous permeation.
*A case was difficult and was finished on the way.
very important. By early stomach cancer treatment study group, they have established a risk-scoring system, termed the “eCura system,” for the risk stratification of lymph node metastasis in patients who have received noncurative ESD for early gastric cancer.\(^{1,43}\) The eCura system seems to be useful for selection of a treatment policy after ESD for elderly people.

In our hospital, treatment decisions for elderly patients are made with regard to ADL, PS, age, and comorbidities. We believe that prior to surgery, the patient concerned and his or her family members should be fully informed of the significance of treatment, as well as possible procedural accidents. Furthermore, informed consent should be obtained.

There are several limitations for this study. First, it was a retrospective study and performed at a single center, which may introduce bias into the results of the study. Second, the number of patients in the super-elderly patients is small. Third, technical problems by ESD operators may have a considerable impact on complications. Fourth, we did not compare survival rates in super-elderly patients between those who underwent ESD and those who did not. However, even considering these limitations, the results of this study are clinically meaningful.

In conclusion, ESD appears to be safely performed, even in elderly patients. In contrast, when performing ESD although further examination is needed with regards to the indications, criteria for determining whether or not to perform additional surgery in the future.

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