

Endoscopic submucosal dissection in early gastric cancer in elderly patients and comorbid conditions

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Abstract

The prognosis of early gastric cancer (EGC) is good if there is no concomitant lymph node metastasis. Therefore, the early detection of EGC is important to improve the prognosis of patients with gastric cancer. In Japan, 40% to 50% of all gastric cancers are EGC, and endoscopic submucosal dissection (ESD) is widely accepted as a local treatment for these lesions, particularly for large lesions that at one time were an indication for gastrectomy because of the difficulty of *en-bloc* resection. Consequently, this procedure can preserve the entire stomach and the patient's postoperative quality of life. ESD has become a general technique with improved procedures and devices, and has become the preferred treatment for EGC rather than gastrectomy. Therefore, ESD may demonstrate many advantages in patients who have several comorbidities, particularly elderly population, patients taking antithrombotic agents, or patients with chronic kidney disease, or liver cirrhosis. However, it is not yet clear whether patients with both EGC and comorbidities are feasible candidates for ESD and whether they would consequently be able to achieve a survival benefit after ESD. In this review, we discuss the clinical problems of ESD in patients with EGC and those comorbid conditions.

Key words: Endoscopic submucosal dissection; Gastric cancer; Elderly person; Antithrombotic agents; Liver cirrhosis; Chronic kidney disease

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Core tip: Endoscopic submucosal dissection (ESD) is widely accepted as a local treatment for gastric cancer, particularly for early gastric cancer. Consequently, this procedure can preserve the entire stomach and the patient's postoperative quality of life. Therefore, ESD

may demonstrate many advantages in patients who have several comorbidities. However, it is not yet clear whether patients with both early gastric cancer (EGC) and comorbidities are feasible candidates for ESD and whether they would consequently be able to achieve a survival benefit after ESD. In this review, we discuss the clinical problems of ESD in EGC in elderly patients and patients with comorbid conditions.

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INTRODUCTION

Gastric cancer is the fourth most common cancer and the second most common cause of cancer-related death in both sexes worldwide^[1,2]. The incidence of gastric cancer has declined in younger populations along with decreasing infection rates of *Helicobacter pylori* (*H. pylori*). The infection rate of *H. pylori*, however, remains high in elderly Asian populations. In 2002, nearly 1 million new cases of gastric cancer were diagnosed, and more than half of these cases were from East Asia, including 41% from China and 11% from Japan^[3]. Therefore, gastric cancer remains one of the most common cancers in Asian countries^[4]. Patients with advanced gastric cancer have a poor prognosis; however, the prognosis of early gastric cancer (EGC) is good^[5,6], and the 5-year gastric cancer-specific survival rate was reportedly 99% in cases that lacked concomitant lymph node metastasis^[7]. EGCs account for 40% to 50% of all gastric cancers in Japan. Endoscopic resection (ER) is an alternative to surgery for treatment of mucosal neoplasms^[8]. The criteria for ER for EGC was classified into the following three groups proposed by Gotoda *et al*^[9] based on the characteristics of the initially detected tumor: "guideline group", "expanded guideline group" and "non-curative group". The guideline group was defined as mucosal differentiated cancer with the largest diameter measuring ≤ 20 mm. In Japan, ER is definitely indicated for this group. The expanded guideline group was defined as the following: (1) mucosal differentiated cancer measuring > 20 mm in diameter; (2) mucosal differentiated cancer with ulceration and measuring ≤ 30 mm in the largest diameter; and (3) differentiated cancer measuring ≤ 30 mm in the largest diameter with a submucosal invasion depth of < 500 μm . If the lesions did not meet these criteria, they were classified as the non-curative group. ER includes endoscopic mucosal resection (EMR) and endoscopic

submucosal dissection (ESD)^[10]. EMR has been a standard technique for early gastric cancer with no risk of lymph node metastasis. EMR is, however, reportedly difficult to achieve *en-bloc* complete resection for the removal of lesions with the extended indication^[11]. ESD is widely accepted as a treatment for EGC, particularly for larger lesions that at one time were an indication for gastrectomy because of the difficulty of *en-bloc* resection. Consequently, this procedure can preserve the entire stomach and improve the patient's postoperative quality of life. Moreover, ESD has become a standard technique with improved procedures and devices. Now, EMR has been replaced by ESD.

Because most patients with EGC are elderly, these patients commonly have several comorbidities that involve medical treatment, such as antithrombotic agents to combat thrombosis, chronic kidney disease, or liver cirrhosis. In this review, we discuss the clinical problems associated with ESD in patients with EGC and comorbid conditions.

ELDERLY PATIENTS

Most patients with gastric cancer are diagnosed between their late 60s and 80s^[12]. Therefore, most patients with EGC are elderly and therefore have an increased risk for procedure-related complications or events. EGCs generally grow slowly, and thus, we must determine a therapeutic strategy that considers the presence of comorbid diseases.

Most of elderly individuals have multiple chronic medical conditions^[13]. Therefore, any indication for elderly patients with EGC must account for both life expectancy and concomitant conditions or diseases. However, there is little evidence that endoscopic resection is well tolerated in the elderly EGC patients who are most likely to benefit from resection.

Kakushima *et al*^[14] previously reported the safety and efficacy of ESD for EGC in elderly patients aged 75 years or older (average age, 79 years old). Indeed, 57% of these patients also presented with comorbid diseases, but the *en-bloc* plus R0 resection rate and the complication rate in elderly patients were not significantly different from those of younger patients. Kakushima *et al*^[14] concluded that ESD for gastric neoplasms is safe and effective in both elderly patients and younger patients. We also retrospectively validated whether gastric ESD was feasible even for elderly patients. In a study of 459 patients aged 75 years or older among 1188 EGC patients, perforation occurred in 20 patients (4.4%), and bleeding occurred in 12 patients (2.6%)^[15]. The incidences of those complications were similar to those in the younger patients. Advanced age (*i.e.*, older than 75 years), however, is associated with an increased risk for postoperative pneumonia. Toyokawa *et al*^[16] reported that the rate of late bleeding rate was significantly higher in elderly patients aged 75 years or compared with

Table 1 Endoscopic submucosal dissection in elderly patient *n* (%)

Ref.	Age (yr)	Patients <i>n</i> , lesions <i>n</i>	En-bloc resection, with RO, %	Perforation	Late bleeding	Pneumonia
Hirasaki <i>et al</i> ^[53]	≥ 75	53, 53	96, 81	1 (1.9)	(43%) ¹	NE
Kakushima <i>et al</i> ^[14]	≥ 75	42, 49	NE, 96	1 (2)	3 (7)	NE
Akasaka <i>et al</i> ^[15]	≥ 75	459, 459	NE	20 (4.4)	12 (2.6)	15 (3.3)
Toyokawa <i>et al</i> ^[54]	≥ 75	200, 229	92, 80	4 (1.7)	22 (9.6)	2 (0.87)
Abe <i>et al</i> ^[55]	≥ 80	440, 470	NE, 77.9	12 (2.8)	14 (3.2)	NE
Park <i>et al</i> ^[17]	≥ 70	132, 132	NE	6 (4.5)	5 (3.8)	6 (4.5)
Zhang <i>et al</i> ^[56]	≥ 75	171, 187	98, 94.1		(15.2%) ²	NE

¹Bleeding was defined in cases that required endoscopic management with methods such as clip placement and/or monopolar electrocoagulation to stop the bleeding, including early and late bleeding. One patient required surgery to treat the bleeding; ²Immediate bleeding. NE: Not evaluated.

younger patients (9.6% vs 5.3%, $P = 0.0473$). After a multivariate analysis, the size of the resected specimen was the only significant risk factor for delayed bleeding. Recently, Park *et al*^[17] reported that with expanded criteria as proposed by Gotoda *et al*^[18], overall survival did not differ between elderly patients with EGC who underwent ESD and those who underwent surgery, although the risk of metachronous lesions was higher in patients who underwent ESD^[17]. A propensity-matched analysis indicated that all of the adverse events observed in the ESD group were successfully treated and did not result in mortality. In contrast, two patients in the surgery group died of operation surgery-related complications, although no significant difference was observed between the two groups. Based on these data, we believe that gastric ESD in elderly patients is feasible and that EGC is manageable with this treatment (Table 1).

PATIENTS TREATED WITH ANTITHROMBOTIC AGENTS

In the last few decades, the number of patients treated with oral antithrombotic agents, including antiplatelet agents and anticoagulants, has increased worldwide in an effort to prevent or reduce thromboembolic events^[19]. Recently, many novel oral anticoagulant drugs have been presented as alternatives to vitamin K antagonists and are either currently available or in the early or advanced stages of clinical development^[20].

In patients who undergo minor surgical procedures, the discontinuation of antithrombotic therapy may not be required. However, patients who undergo major surgical procedures are required to discontinue the use of these drugs to minimize their risk for perioperative bleeding, as the continuation of antithrombotic agents in the perioperative period may lead to an increased risk of bleeding. In endoscopic procedures, antithrombotic

agents may be discontinued when a patient is judged to have a low risk of thrombosis. The appropriate cessation of antithrombotic therapy has recently been reported to not increase the rate of delayed bleeding^[21,22]. However, when gastric ESD is scheduled in a patient treated with oral anticoagulants (*e.g.*, warfarin) and judged by the prescribing doctor to have a high risk of thromboembolism, he or she will also undergo heparin replacement (HR). Similarly, when gastric ESD is scheduled in a patient treated with antiplatelet agents (*e.g.*, aspirin, ticlopidine, clopidogrel and cilostazol) and judged to have a high risk of thromboembolism, he or she will be placed on a continuous aspirin or cilostazol regime according to recently published guidelines from the Japan Gastroenterological Endoscopy Society^[23]. In patients at high risk of thrombosis, the risks of both bleeding and thrombosis are unclear in patients who undergo endoscopic invasive procedures, such as gastric ESD.

Regarding antiplatelet agents, the continuous use of aspirin during the perioperative period of ESD has been reported to be acceptable, although the rate of delayed bleeding is slightly higher^[24,25]. In an analysis of the combination of antiplatelet agents and anticoagulants, Koh *et al*^[26] reported that antithrombotic therapy increased the risk of delayed bleeding. Takeuchi *et al*^[27] also reported that the rate of postoperative bleeding in patients taking antithrombotic agents was 23.3%, which is significantly higher than the 2.0% observed in patients not treated with antithrombotic agents. Despite the discontinuation of antithrombotic agents, the authors found that combination therapy of low-dose aspirin (LDA) plus warfarin was a significant predictor of post-ESD bleeding (OR = 14.83, $P < 0.001$).

We believe that not only is LDA plus warfarin combination therapy a risk factor for late bleeding but also that HR is a risk factor for this condition. HR therapy is used as a bridge therapy along with invasive treatments to prevent antithrombotic events. We previously showed that the rate of delayed bleeding was high during gastric ESD (38%)^[22] or colon polypectomy (20.0%)^[28] under HR therapy.

However, few studies on the relationship between thrombotic events and endoscopic procedures have been conducted. The incidence rates of thrombotic events related to gastric ESD have been reported to range from 0 to 4.2%^[21,22,24,27] (Table 2). We encountered one patient (4.2%) with delayed bleeding in the HR group who experienced a thrombotic event^[22]. The patient's activated partial thromboplastin time was sufficiently prolonged under HR after successful endoscopic hemostasis for late bleeding. Although the patient discontinued the use of all antiplatelet agents, a cerebral infarction developed on post-operative day 13. Therefore, thrombosis during bleeding should be carefully considered, despite the presence of a sufficient anticoagulant effect during the perioperative period (Table 2).

Table 2 Endoscopic submucosal dissection in patients treated with antithrombotic agents *n* (%)

Ref.	Patients <i>n</i> , lesions <i>n</i>	En-bloc resection, with RO, %	Perforation	Late bleeding	HR No., bleeding	Thrombotic event
Ono <i>et al</i> ^[21]	47 ¹ , 56	96.4/82.1	1 (1.8)	6 (10.7)	1, 3 (33)	0 (0)
Lim <i>et al</i> ^[24]	274, ND	NE	0 (0)	26 (12.6) ²	NA	1 (0.5) ³
Koh <i>et al</i> ^[26]	175, ND	NE	NE	17 (9.7) ⁴	NA	0 (0)
Takeuchi <i>et al</i> ^[27]	90, 90	NE	NE	21 (23.3) ⁵	12, 21 (57)	1 (1)
Yoshio <i>et al</i> ^[22]	24, 24	100/100	0 (0)	9 (38) ⁶	9, 24 (38)	1 (4.2)

¹Forty-four low-risk patients stopped treatment with antithrombotic agents for 1 wk before and after endoscopic submucosal dissection (ESD). Three high-risk patients underwent intravenous heparin replacement during the cessation period; ²A total of 274 patients were treated with antiplatelet medication, 102 of whom discontinued the use of these drugs for 7 d or more before ESD, whereas the remaining patients continued use; ³One (1%) of the 102 patients who discontinued the use of antiplatelet medication developed an acute cerebral infarction; ⁴Antithrombotic drug therapy was principally interrupted preoperatively and restarted when hemostasis was confirmed by second-look endoscopy. The rate of early postoperative bleeding during the first 5 postoperative days was 4%, and the rate of subsequent bleeding was 5.7%; ⁵All patients commenced treatment with proton pump inhibitors immediately following surgery. Antiplatelet agents were discontinued for 7 d preoperatively until postoperative day 1, and anticoagulants were discontinued for 5 d preoperatively until postoperative day 1. A total of 46 patients received low-dose aspirin (LDA) only, 23 received LDA + thienopyridine, and 21 received LDA + warfarin. Anticoagulants were discontinued from preoperative day 4 to postoperative day 2. Heparin was substituted for anticoagulants after the latter were discontinued; ⁶All patients underwent intravenous heparin replacement during the cessation period because of an increased risk of thromboembolism. HR: Heparin replacement; NA: Not applicable; NE: Not evaluated.

CHRONIC KIDNEY DISEASE

Chronic kidney disease (CKD) is associated with significant morbidity and mortality and is now recognized as a worldwide problem because the number of patients with CKD is sharply increasing^[29]. In Japan, clinical practice guidelines have reported that the frequencies of stage 1, 2, 3, and 4/5 CKD in adults were 0.6%, 1.7%, 10.4% and 0.2%, respectively, in 2009. The total number of patients in stages 3 to 5 was estimated to be approximately 10.97 million^[30]. Renal function linearly deteriorates with age. Therefore, the number of patients with CKD is higher in elderly populations, and consequently, the number of patients with gastric cancer and CKD is also believed to be increasing. Patients with CKD are more likely to experience multiple complications during the surgical procedure, such as procedure-related bleeding due to uremic platelet dysfunction and tissue vulnerability, compared with patients without CKD^[31,32]. The safety and feasibility of gastric ESD for patients with CKD, however, are unclear.

Mannen *et al*^[33] reported no significant risk factors for complications from gastric ESD among 17 patients

Table 3 Endoscopic submucosal dissection in patients with chronic kidney disease *n* (%)

Ref.	CKD, <i>n</i> /lesions, <i>n</i>	Hemo-dialysis, <i>n</i>	HR, <i>n</i>	En-bloc resection, with RO, %	Perforation	Late bleeding
Goto <i>et al</i> ^[34]	7/9	7	ND	100/100	0 (0)	1 (14)
Kwon <i>et al</i> ^[35]	17 ¹ /19	8	ND	94.7/94.7	0 (0)	3 (17.6) ²
Numata <i>et al</i> ^[36]	63 /79	12	2	89.9/89.9	3 (4.8)	11 (17.5) ³
Yoshioka <i>et al</i> ^[37]	144/ 144	19	7	95.8/86.1	6 (4.2)	8 (5.6)

¹Includes 2 patients with peritoneal dialysis; ²Original paper reported 15.5%, which represented the percentage of perforation per lesion; ³The rate of late bleeding was 33.3% (5/15) in hemodialysis patients and 9.4% (6/64) in non-hemodialysis patients; the difference was significant ($P < 0.05$). ND: Not described; HR: Heparin replacement.

with CKD. Goto *et al*^[34] reported complications from gastric ESD in 7 patients with CKD who underwent hemodialysis (HD), one patient experienced delayed bleeding that required a blood transfusion, followed by shunt occlusion. Although all of the lesions were resected *en-bloc* with RO resection, the authors concluded that ESD in patients with CKD should be carefully considered for substantial risks because late-onset complications may turn out to be severe. Kwon *et al*^[35] also conducted a single-center retrospective study in which 17 patients with CKD were compared with 894 control patients who received gastric ESD. They reported no significant differences in *en-bloc* resection and perforation rates between patients with CKD and patients without CKD, but a tendency to hemorrhage was observed in patients with CKD. Numata *et al*^[36] reported that the rate of post-ESD bleeding was 33% in 15 lesions in 12 patients with HD among the 63 patients with CKD, whereas the rate of post-ESD bleeding was only 9% in patients without HD. In addition, 2 deaths related to the ESD procedure were reported, but no deaths due to EGC occurred. Both of these patients were receiving HD, and the deaths occurred subsequent to the bleeding. The authors concluded that the cause of the bleeding was associated with other comorbidities, such as the use of anticoagulants during HD^[36]. To focus on the eGFR, we also evaluated 144 patients with CKD in a multicenter survey that included municipal hospitals, where many patients with CKD were among those who underwent ESD^[37]. In our study, we included patients with gastric cancer under the expanded criteria^[7], and found that 20 patients did not achieve curative resection (13.9%), whereas additional surgeries were performed in 14 patients (9.7%). No ESD-related deaths were reported in these 144 patients. With respect to short-term outcomes, late bleeding was observed in 1.1% of patients in stage 3 (1/92), 13.0% in stage 4(3/23), and 13.8% in stage 5 (4/29). All incidences of bleeding were controlled by endoscopic hemostasis, but 5 patients required a blood transfusion (3.5%). In a univariate Poisson regression analysis including CKD stage, HD, diabetes mellitus, use of antithrombotic

Table 4 Endoscopic submucosal dissection in patients with liver cirrhosis

Ref.	Patients N (Child-Pugh A, B, C) /lesion, n	<i>En-bloc</i> resection, with RO, %	Perforation n (%)	Late bleeding n (%)	Median observation period (mo) Prognosis
Ogura <i>et al</i> ^[51]	15 (9, 6, 0)/18	88.9, 77.8	0 (0)	3 (20)	21.4 mo No recurrence but 3 patients underwent additional ER or surgery NE
Kwon <i>et al</i> ^[35]	18 (13, 3, 2)/22	90.9, 86.4	1 (5.6)	ND (approximately 9)	
Choi <i>et al</i> ^[57]	23 (20, 3, 0)/23	86.2, 82.6	0 (0)	1 (4.3)	17.5 mo (range, 2 to 72 mo) No local recurrence was found in either group during the follow-up period
Repici <i>et al</i> ^[58]	5 (4, 1, 0) /5	100, 100	0 (0)	2 (40)	22 mo (range, 18 to 36 mo) No recurrence
Kato <i>et al</i> ^[52]	69 (53, 15, 1)/69	99, 90	1 (1.5)	4 (5.8)	33.4 mo (range, 0.5-96.9 mo) The 5-yr overall survival rates were 60%

ND: Not described; NE: Not evaluated.

agents and HR, the critical factors related to bleeding were CKD stage and HD. In multivariate Poisson regression analyses, the risk ratio of bleeding was 11.4 in patients with stage 4 CKD and 11.0 in patients with stage 5 CKD. Thus, we concluded that CKD calculated from the eGFR would be an independent risk factor regardless of whether a patient undergoes HD^[37].

Gastric ESD in patients with CKD is technically feasible, even in patients undergoing HD. However, bleeding in patients with CKD may lead to death due to other comorbidities, such as conditions that require the use of anticoagulants. Therefore, particular attention should be paid to late bleeding in patients with CKD, particularly patients with advanced CKD (Table 3).

LIVER CIRRHOSIS

Liver cirrhosis (LC) is a common disease, especially in Japan and other East Asian countries, due to the high prevalences of hepatitis B virus (HBV) and hepatitis C virus (HCV) infections^[41]. *H. pylori* and HBV/HCV, respectively, are the leading causes of bacterial and viral diseases in humans worldwide, particularly in East Asian. Consequently, it is not rare for patients to be affected by these two diseases. Patients with LC have a poor prognosis because of liver failure or the development of hepatocellular carcinoma (HCC)^[38], esophagogastric varices^[39], compromised host^[40], or glucose intolerance^[41]. In contrast, the prognosis of patients with EGC is good^[7]. Therefore, it is difficult to determine whether patients with cirrhosis and EGC are suitable for ESD because this procedure may not increase the survival benefit for patients with LC. Until now, several studies have focused on the clinical outcomes of radical gastrectomy in patients with gastric cancer and comorbid LC^[42-47]. These studies indicate that 10%-20% of patients with LC develop postoperative intractable ascites, and that the perioperative mortality rate is approximately 10%. However, few investigators have reported whether gastric ESD can be performed safely in patients with poor liver function or gastric varices. During gastric

ESD, the rate of bleeding rate may increase because LC is frequently accompanied by complex alterations in the hemostatic system^[48,49], and patients with LC have fewer platelets and a prolonged prothrombin time. More specifically, it is technically difficult to perform ESD when a varix is located near a gastric lesion. Kim *et al*^[50], however, reported a successful ESD adjacent to a fundal varix after treatment with endoscopic variceal obturation using N-butyl-2-cyanoacrylate (Histacryl[®]).

Ogura *et al*^[51] performed a case series study on short-term ESD outcomes for 18 patients with LC. The authors reported that *en-bloc* resection was achieved in 88.9% of patients with EGC and cirrhosis but that the rate of late bleeding rate appeared to be higher (20%). Kwon *et al*^[35] reported that the procedure time and short-term outcomes in patients with cirrhosis, such as the rates for *en-bloc* and complete resections, did not differ from those of the control group, even though the results of endoscopic mucosal resection were included. Immediate bleeding tended to occur more frequently in patients with both LC and CKD than in controls (47.5% vs 33.9%, $P = 0.077$). However, no significant difference was observed in the incidence of perforation^[35]. We also evaluated outcomes of gastric ESD among 69 patients with LC. Based on a propensity-matched analysis, 53 (77%) of these patients had Child Pugh Grade A (CP-A) and 16 (28%) had Child Pugh Grade B/C (CP-B/C) compared with patients without LC^[52]. In that study, short-term outcomes did not differ between the patients with LC and controls or between the patients with CP-A and those with CP-B/C. This study, however, revealed that the CP grade and HCC history were significantly independent risk factors for poor prognoses according to a Cox proportional hazards model. Patients with cirrhosis and CP-A demonstrated an overall survival that was nearly equivalent to that of patients without cirrhosis; however, patients with cirrhosis and CP-B/C or with histories of HCC had significantly worse long-term outcomes (the overall 3- and 5-year survival rates after ESD were 58% and 26%, respectively). Therefore, the long-term outcomes of patients with cirrhosis were likely influenced by liver

function or cirrhosis-related conditions rather than by gastric cancer. We concluded that patients with cirrhosis and CP-A appear to be good candidates for ESD but that patients with CP-B/C or with histories of HCC benefit less from ESD (Table 4).

CONCLUSION

This review demonstrated that gastric ESD could be performed safely, even in medically complex patients, such as elderly patients, those who are being treated with antithrombotic agents, and those with CKD or LC regarding the risk of complication, particularly bleeding. Although the short-term outcomes were not inferior, ESD was less beneficial to the survival of patients with a poor prognosis.

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