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ORIGINAL ARTICLE

Long-term outcomes and prognostic factors with non-curative endoscopic submucosal dissection for gastric cancer in elderly patients aged ≥ 75 years

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Abstract

Background Little is known about the long-term outcomes and prognostic factors with non-curative endoscopic submucosal dissection (ESD) in elderly patients with early gastric cancer.

Methods Clinicopathological findings and long-term outcomes were evaluated in 87 patients with early gastric cancer (EGC) aged ≥ 75 years who were treated with non-curative ESD. Prognostic factors for overall survival (OS) were analyzed with the Kaplan–Meier method and a Cox proportional hazards model.

Results During the follow-up period, among 27 patients who died of any cause, only one patient died of gastric cancer. OS probabilities after 3 and 5 years were 89.7% and 79.3%, respectively. Univariate analyses revealed that Eastern Cooperative Oncology Group performance status 2–3, Charlson comorbidity index (CCI) ≥ 3, neutrophil/lymphocyte ratio ≥ 3.3, prognostic nutritional index < 44.8, distal tumor location and macroscopically depressed or flat configuration were associated with poor OS. Cox multivariate analysis revealed high CCI (≥ 3) to be an independent prognostic factor associated with OS (hazard ratio: 2.63, 95% confidence interval [CI] 1.06–6.49, $P = 0.037$).

Conclusions CCI may be a useful parameter for decision-making regarding additional surgery for elderly patients with gastric cancer treated by non-curative ESD.

Keywords Gastric cancer · Elderly patients · Prognostic factors · Charlson comorbidity index

Introduction

In recent decades, the size of the elderly population has been increasing rapidly worldwide. Gastric cancer is still a frequent cause of death in Japan. Endoscopic submucosal dissection (ESD) is an established, standard treatment for early gastric cancer (EGC) [1–5]. ESD is accepted as a less invasive treatment and provides improvement in postoperative quality of life compared to open surgery [6, 7]. In addition, a number of studies have revealed excellent short and long-term outcomes after ESD for EGC, even in elderly patients [8–14]. Due to the increasing necessity of ESD for elderly patients, however, physicians are facing the problem of how to decide whether to perform additional gastrectomy in elderly patients with EGC who undergo non-curative ESD.

To date, several studies have reported the clinical outcomes of EGC cases after non-curative ESD [15–19]. However, only a few studies have reported the long-term outcomes with non-curative ESD in elderly patients. In addition, elderly patients have higher rates of all-cause mortality than younger patients. The aim of this study was to clarify

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the long-term outcomes and prognostic factors with non-curative ESD for EGC in elderly patients.

Methods

Patients

We performed ESD for 1358 patients with EGC at our institute between June 2002 and December 2012. Among these 1358 patients, 39 patients with remnant stomachs, 4 patients with gastric tubes, and 103 patients of unknown status were excluded. Of the remaining 1212 patients, 1008 patients who met the curability criteria were excluded. Of the remaining 204 patients, 87 patients aged ≥ 75 years were the subjects of the present study (Fig. 1).

Patient medical charts were reviewed to obtain data on clinical and demographic characteristics, including age, gender, Eastern Cooperative Oncology Group (ECOG) performance status (PS) [20], and body mass index (BMI). We evaluated the following items as possible prognostic factors: Geriatric Nutritional Risk Index (GNRI) [21, 22], Charlson comorbidity index (CCI) [23], neutrophil to lymphocyte ratio (NLR) [24] and prognostic nutritional index (PNI) [25]. The GNRI was calculated with the values of serum albumin and BMI listed on patient medical charts just before ESD: GNRI = 14.89 × serum albumin (g/dL) + 41.7 × BMI/22 [22]. The CCI was calculated with scores based on the original definition [23]. The NLR was calculated by dividing the total neutrophil count by the total lymphocyte count [24]. The PNI was calculated with the serum albumin level and the total lymphocyte count: PNI = 10 × serum albumin (g/dL) + 0.005 × total lymphocyte count (per mm^3) [25]. Written informed consent was obtained from all patients before ESD. This study protocol was approved by the ethical committee of Iwate Medical University (H29-182).

Curability criteria

Curability of ESD was determined on the basis of guidelines reported by the Japanese Gastric Cancer Association [26] and the Japanese Gastroenterological Endoscopy Association [27]. When a lesion was resected en bloc, was < 2 cm in diameter, and was predominantly a differentiated type, pathologically intramucosal carcinoma (pT1a), lacking in ulcerative findings (UL[−]) and lymphovascular invasion (ly0, v0), with negative surgical margins (R0), the procedure was considered a curative resection by absolute indication. When a lesion was resected en bloc and was (1) ≥ 2 cm in diameter, predominantly a differentiated type, pT1a, and UL(−); (2) < 3 cm, predominantly a differentiated type, pT1a, and UL(+); (3) < 2 cm, predominantly an undifferentiated type, pT1a, and UL(−); or (4) < 3 cm, predominantly a differentiated type, pathologically minute submucosal (SM) cancer < 500 μm (pT1b/SM1) in vertical depth, and with negative surgical margins (R0), the procedure was considered a curative resection by the expanded indications. When a lesion did not meet the criteria of the absolute or the expanded indications, the procedure was considered a non-curative resection, as described previously [19].

Follow-up and collection of outcome data

The selection of either additional gastrectomy or follow-up without gastrectomy was determined by the chief physician for each patient in consideration of the risk of gastrectomy. For patients who underwent additional gastrectomy, endoscopic examination was conducted once a year, and computed tomography (CT) was performed 6 months after gastrectomy, and thereafter once a year. For patients who were followed without gastrectomy, endoscopic examination was conducted 1–3 months after ESD. *Helicobacter pylori* (*H.*

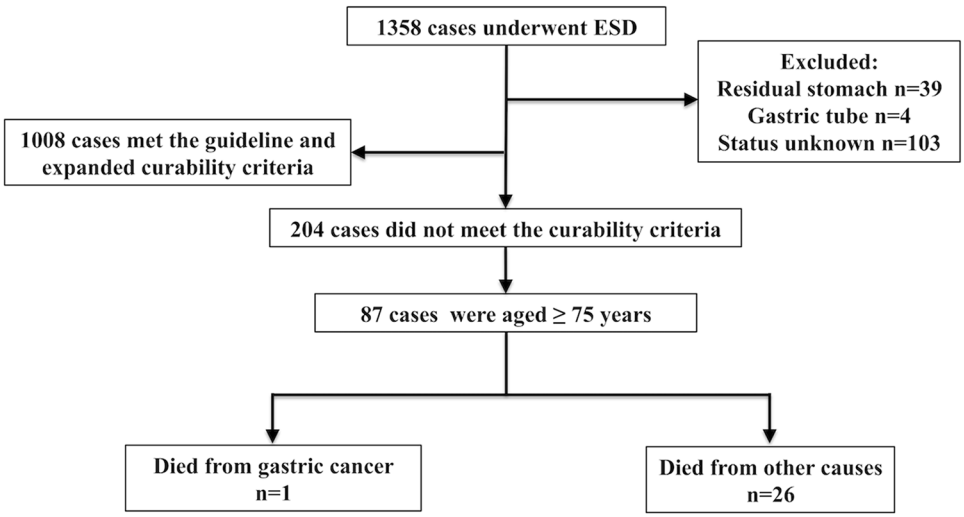

Fig. 1 Flow of patients enrolled in the study

pylori) was eradicated in infected patients. Thereafter, endoscopic examinations were conducted at 6 and 12 months. Unless local recurrence was found, yearly endoscopic examination was continued. Abdominal ultrasound and CT were also performed once a year. For patients who were followed up outside of our institution, we conducted an annual questionnaire survey via their primary care physicians. If patients had not made hospital visits, we contacted them or their family members directly to confirm the prognosis.

Statistical analysis

Overall survival (OS) after ESD was analyzed with the Kaplan–Meier method, and the differences between groups were assessed by the log-rank test. The relationship between OS and each clinicopathologic factor was analyzed by univariate analysis with the log-rank test. Cut-off values for the GNRI were determined based on a previous report [21]. Cut-off values for the NLR and PNI were determined by receiver operating characteristic (ROC) analysis. Values that maximized the sensitivity and specificity for 5-year OS were used as the cut-off values. Possible prognostic factors were included in multivariate analyses with a Cox proportional hazards regression model. A P value < 0.05 was considered to be statistically significant. All of the statistical analyses were performed with SPSS version 22 software for MAC OS (SPSS Inc., Chicago, IL, USA) and JMP version 12 (Statistical Discovery Program, Cary, NC, USA).

Results

Table 1 shows the demographic and clinical characteristics of the study population. The median age was 78 years, and most patients were male (74.7%). The ECOG PS was 0 or 1 in 66 patients (75.9%). The median BMI was 22.7 kg/m^2, and the median follow-up period was 6.7 years. The mean GNRI was 103.4, and 66 patients (75.9%) had a CCI of 0–2. The median NLR was 2.3, and the mean PNI was 48.1.

The clinicopathological characteristics of the resected EGCs are summarized in Table 2. Of the 87 tumors, 81 (93.1%) were initial cancers and 6 (6.9%) were metachronous cancers. The most frequent location was the middle third portion of the stomach, and the median tumor size was 23 mm. Most tumors were the histologically differentiated type (92%), and 24 tumors (27.6%) had invaded the deep portion of the submucosa. Lymphovascular invasion was positive in 26 tumors (29.9%), and ulcerative findings were noted in 18 tumors (20.7%). The median procedure time for ESD was 66 min. As for adverse events, postoperative bleeding was observed in one (1.1%) patient and perforation was observed in five (5.7%) patients.

Table 1 Demographic and clinical characteristics of 87 patients aged ≥ 75 years who underwent non-curative ESD for gastric cancer

Age, years, median (range, IQR)	78 (75–88, 7)
Gender, *n* (%)	
Male	65 (74.7)
Female	22 (25.3)
ECOG PS, *n* (%)	
0	28 (32.2)
1	38 (43.7)
2	19 (21.8)
3	2 (2.3)
Body mass index, kg/m^2, median (range, IQR)	22.7 (16.2–33.3, 3.3)
Follow-up period, years, median (range, IQR)	6.7 (0.1–14.8, 3.8)
GNRI, mean (± SD)	103.4 (± 9.7)
CCI, *n* (%)	
0	30 (34.5)
1	24 (27.6)
2	12 (13.8)
3	15 (17.2)
4	3 (3.4)
5	2 (2.3)
6	1 (1.1)
NLR, median (range, IQR)	2.3 (0.6–11.9, 1.3)
PNI, mean (± SD)	48.1 (± 5.3)

ESD endoscopic submucosal dissection, *IQR* inter-quartile range, *ECOG PS* Eastern Cooperative Oncology Group performance status, *SD* standard deviation, *GNRI* geriatric nutritional risk index, *CCI* Charlson comorbidity index, *NLR* neutrophil to lymphocyte ratio, *PNI* prognostic nutritional index

Additional gastrectomy was performed in 26 patients (29.9%), of whom 20 patients underwent distal gastrectomy, and 6 patients underwent total gastrectomy. The final histopathologic findings were as follows: 7 patients had residual cancer, and another patient had lymph node metastasis. In the remaining 19 patients, neither residual cancer nor lymph node metastasis was found.

During the follow-up period, recurrence of primary EGC was found in two patients. A patient was found to have local recurrence after ESD with positive horizontal margin. This patient was treated by additional ESD without subsequent recurrence. The other patient was treated by gastrectomy after ESD because of submucosal invasion and positive lymphatic permeation. The patient died of peritoneal dissemination of the primary EGC 2 years after the surgery.

Metachronous gastric cancers were observed in 8 patients (9.2%). All 8 patients had been successfully treated with additional ESD. During the follow-up period, among 27 patients who died, only one patient died of gastric cancer. Probabilities of OS after 3 and 5 years were 89.7% and 79.3%, respectively.

Results of univariate analyses for possible prognostic factors are summarized in Table 3. Patients who had ECOG PS 2–3, high CCI (≥ 3), high NLR (≥ 3.3), low

Table 2 Clinicopathological characteristics of 87 patients aged ≥ 75 years who underwent non-curative ESD for gastric cancer

Tumor type, *n* (%)	
Primary cancer	81 (93.1)
Metachronous cancer	6 (6.9)
Tumor location, *n* (%)	
Upper	22 (25.3)
Middle	42 (48.3)
Lower	23 (26.4)
Tumor size, mm, median (range, IQR)	23.0 (3–95, 22)
Macroscopic appearance, *n* (%)	
Elevated	46 (52.9)
Depressed/flat	41 (47.1)
Histology, *n* (%)	
Differentiated type	80 (92.0)
Undifferentiated type	7 (8.0)
Depth of invasion, *n* (%)	
M/SM1	63 (72.4)
SM2	24 (27.6)
Lymphovascular invasion, *n* (%)	26 (29.9)
Ulcerative findings, *n* (%)	18 (20.7)
Procedure time, min, median (range, IQR)	66 (8-632, 78)
Adverse events	1 (1.1)
Postoperative bleeding, *n* (%)	
Perforation, *n* (%)	5 (5.7)
Additional gastrectomy, *n* (%)	26 (29.9)
Lymph node metastasis, *n* (%)	1 (1.1)
Other metachronous cancers, *n* (%)	8 (9.2)
Prognosis	27 (31.0)
Death due to any causes, *n* (%)	
Death due to gastric cancer, *n* (%)	1 (1.1)

ESD endoscopic submucosal dissection, *IQR* inter-quartile range, *M* mucosa, *SM1* superficial portion of the submucosa within 500 μm from the muscularis mucosae, *SM2* deep portion of the submucosa ≥ 500 μm from the muscularis mucosae, *min* minutes

PNI (< 44.8), tumor location in the lower portion of the stomach and depressed/flat type of macroscopic configuration had worse OS than patients without those factors. Although the difference was not statistically significant, 5-year OS was higher in patients with additional gastrectomy than in those without (0.85 vs 0.77, $P = 0.34$).

Table 4 shows the results of multivariate analysis using a Cox proportional hazards model including possible prognostic factors. As shown in the table, only high CCI (≥ 3) was found to be an independent prognostic factor associated with worse OS (hazard ratio, 2.79; 95% CI 1.16–6.69; $P = 0.021$). The overall survival rate was significantly lower in a high-CCI group than in a low-CCI group (Fig. 2, $P < 0.001$).

Table 3 Overall survival (Kaplan–Meier method)

Variable	No. of patients	5-year OS	*P* value
Age			
≥ 79 years	41	0.73	0.06
< 79 years	46	0.85	
Gender			
Male	65	0.77	0.11
Female	22	0.86	
ECOG PS			
0–1	66	0.85	0.001
2–3	21	0.62	
GNRI			
≥ 92	79	0.78	0.91
< 92	8	0.75	
CCI			
0–2	66	0.88	< 0.001
≥ 3	21	0.52	
NLR			
≥ 3.3	13	0.54	0.002
< 3.3	74	0.84	
PNI			
≥ 44.8	67	0.85	0.021
< 44.8	20	0.60	
Tumor location			
Upper	22	0.86	0.047
Middle	42	0.83	
Lower	23	0.65	
Tumor size			
≥ 20 mm	54	0.74	0.23
< 20 mm	33	0.88	
Macroscopic appearance			
Elevated	46	0.89	0.019
Depressed/flat	41	0.68	
Histology			
Differentiated type	80	0.80	0.90
Undifferentiated type	7	0.71	
Depth of invasion			
M/SM1	63	0.76	0.41
SM2	24	0.88	
Lymphovascular invasion			
Present	26	0.77	0.85
Absent	61	0.80	
Ulcerative findings			
Present	18	0.89	0.96
Absent	69	0.77	
Additional gastrectomy			
Yes	26	0.85	0.34
No	61	0.77	

OS overall survival, *ECOG PS* Eastern Cooperative Oncology Group performance status, *GNRI* geriatric nutritional risk index, *CCI* Charlson comorbidity index, *NLR* neutrophil to lymphocyte ratio, *PNI* prognostic nutritional index, *M* mucosa, *SM1* superficial portion of the submucosa within 500 μm from the muscularis mucosae, *SM2* deep portion of the submucosa ≥ 500 μm from the muscularis mucosae

Table 4 Multivariate analysis of factors associated with overall survival

Variable	HR	95% CI	*P* value
Age ≥ 79 years	1.94	0.87–4.35	0.11
ECOG PS ≥ 2	1.95	0.82–4.67	0.13
CCI ≥ 3	2.79	1.16–6.69	0.021
NLR ≥ 3.3	1.86	0.73–4.74	0.19
PNI ≤ 44.8	1.50	0.60–3.77	0.39

HR hazard ratio, *CI* confidence interval, *ECOG PS* Eastern Cooperative Oncology Group performance status, *CCI* Charlson comorbidity index, *NLR* neutrophil to lymphocyte ratio, *PNI* prognostic nutritional index

Discussion

Several studies have investigated the clinical outcomes of elderly patients with EGC [8–14]. However, long-term outcomes and prognostic factors in elderly patients with EGC were evaluated in only a few studies [10, 12, 14]. To our knowledge, this is the first study to report the long-term outcomes and prognostic factors of elderly patients with EGC after non-curative ESD. In this study, we included various nutritional factors, such as the GNRI, CCI, NLR, and PNI, as possible prognostic factors. As a result, multivariate analysis revealed a CCI ≥ 3 to be an independent prognostic factor for elderly patients with EGC after non-curative ESD.

The CCI is a scoring system for classifying comorbidities that might affect the risk of mortality [23]. It is a simple, readily available method for estimating the risk of death from comorbid diseases. There have been several reports about the usefulness of the CCI as a prognostic factor in nasopharyngeal and gastrointestinal cancers [28–30]. While some have reported the value of the CCI for predicting postoperative complications in gastric cancer [31, 32], only two previous study have evaluated the relationship between the CCI and prognosis in elderly patients with EGC treated with ESD [14, 33].

In this study, only one patient died of gastric cancer among 87 elderly patients with EGC after non-curative ESD during long-term follow-up. Another 26 patients died of causes other than gastric cancer, including cancer of other organs (8 patients), pneumonia (7 patients), cardiovascular disease (6 patients), and others (5 patients). Since most of our patients died of comorbidities other than gastric cancer, the close association between CCI and OS in our patients seems to be reasonable.

The CCI is calculated as the sum of scores defined for several comorbidities [23]. Our present data showed that a CCI ≥ 3 was an independent prognostic factor in elderly patients aged ≥ 75 years with EGC after non-curative ESD. Because scoring of the CCI is easily completed with a simple medical interview, this may be an advantage, especially in elderly patients treated with ESD. In contrast, Sekiguchi et al. [14] reported that the PNI was the most significant prognostic factor after ESD in elderly patients (aged ≥ 85) who underwent gastric ESD. More recently, Iwai et al. [33] reported that both CCI and PNI were associated with the survival rate in patients with EGC treated by ESD, regardless of age. In the present study, the PNI was found to be a prognostic factor on univariate analysis, but it was not a statistically significant prognostic factor on multivariate analysis.

To date, several studies have reported clinical outcomes of patients with EGC after non-curative ESD [15–19]. Our recent study showed that age was an independent prognostic factor associated with OS in patients with non-curative

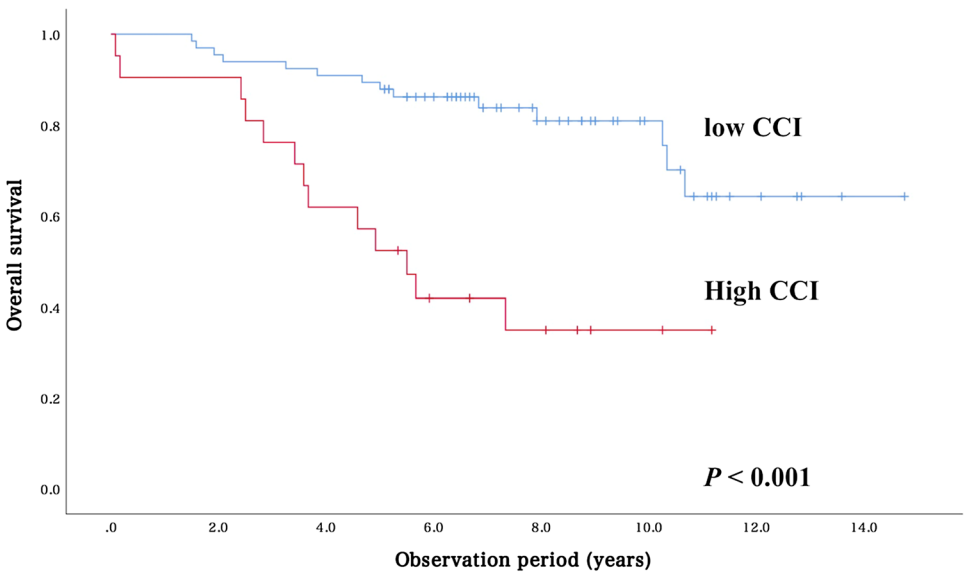

Fig. 2 Overall survival curves for patients in a low-CCI group and a high-CCI group ($P < 0.001$)

gastric ESD with negative resection margins [18]. Kusano et al. [34] analyzed a much greater number of patients treated by gastric endoscopic resection > 75 years of age, and found that OS was significantly higher in patients treated by additional surgery than in the other patients. Although the differences were not statistically significant, 5-year OS was higher in our patients with additional gastrectomy than in those without. We thus believe that additional gastrectomy should not be denied in patients with non-curative gastric ESD. However, our results also seem to suggest that careful follow-up without additional gastrectomy may be a choice in elderly patients ≥ 75 years with high CCI.

Recently, Hatta et al. [35, 36] reported that a risk-scoring system (the eCura system) based on histology of EGC predicted lymph node metastasis (LNM) in patients undergoing radical surgery after non-curative ESD. The system may be useful in decision-making regarding additional treatment after non-curative ESD. However, the value of the eCura system for the prediction of survival in elderly patients with several comorbidities is still unknown. While elderly patients with a low risk of LNM under eCura and a high risk of comorbidities under CCI are candidates for careful follow-up without gastrectomy after non-curative ESD, a stratification system by means of CCI and eCura needs to be elucidated to clarify indications for additional surgery and to predict survival.

The present study has several limitations. First, the retrospective design seems to have introduced selection bias. A prospective study is required to verify the utility of the CCI as a prognostic factor for elderly patients with EGC after non-curative ESD. Second, the sample size was limited, because this study was conducted at a single center. For example, we were unable to explain why tumor location and macroscopic configuration were found to be significant prognostic factors under univariate analyses. A larger, multicenter cohort study seems to be warranted to confirm our findings.

In conclusion, our study showed that a high CCI was an independent prognostic factor related to poor OS in elderly patients aged ≥ 75 years with EGC treated with non-curative ESD. On the basis of the results of this study, CCI is suggested to be a marker for decision-making in additional gastrectomy for elderly patients after non-curative ESD.

Compliance with ethical standards

Conflict of interest The authors declare that they have conflict of interest.

Ethical approval All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. The exemption from informed consent requirement was permitted by Iwate Medical University Institutional Review Board.

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