（資料4）：アンケート調査（患者用）

アンケート調査

患者符号化番号　　[　　]
（担当医が記入する匿名化のための番号です。）
内視鏡切除施行施設　　[　　]（担当医記入）
内視鏡切除施行日　　[　　]（担当医記入）

質問１．
このアンケート調査の記入日をお書き下さい。　　平成　　年　　月　　日

質問２．
内視鏡切除のあとに、上部内視鏡検査（胃カメラ検査）は受けられましたか？○をつけて下さい。

１．はい　　→　付問１．へ

２．いいえ　　→　質問３．へ

付問１．　A. 検査はいつ受けられましたか？　　平成　　年　　月　　日

B. 検査はどこで受けられましたか？　わかる範囲でお答え下さい。

病院

住所

電話番号

担当医　　先生

C. 再発や新たな胃がんが発見されましたか？○をつけて下さい。

１．はい　　→　付問２．へ

２．いいえ　　→　質問４．へ

付問２．　その治療は受けられましたか（受けていますか）？○をつけて下さい。

１．はい　　→　付問３．へ

２．いいえ　　→　質問４．へ

付問３．　その治療はどこで受けられましたか（受けていますか）？
わかる範囲でお答え下さい。

病院

住所

電話番号＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

担当医＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿先生

質問３．

内視鏡切除後に上部内視鏡検査を受けられていない理由は何ですか？○をつけて下さい。

１．転居し、かかりつけの病院に行けなくなった。

２．大きな病気になった。

３．忙しかった。

４．その他　　[　　]

質問４．

ヘリコバクター・ピロリ菌について、○をつけて下さい。

１．感染歴あり　　→　付問４．へ

２．感染歴なし　　→　質問５．へ

３．不明（検査未施行）　→　質問５．へ

付問４．　除菌治療の有無について、○をつけて下さい。

１．除菌施行　　→　付問５．へ

２．除菌未施行　→　質問５．へ

付問５．　A. 除菌治療開始日は？　　平成　　年　　月　　日頃

B. 除菌治療の成否について、○をつけて下さい。

１．除菌成功

２．除菌失敗

３．不明（判定未施行）

質問５．

内視鏡切除を行った後に、新たな大きな病気にかかりましたか？（風邪などの軽い病気は除きます。）○をつけて下さい。

４．はい　　→　付問６．へ

５．いいえ　　→　質問６．へ

付問６．　新たな大きな病気について、すべて記入して下さい。
（記入しきれない場合、裏面にご記入下さい。）

A. いつ頃からですか？　　平成　　年　　月　　頃

B. 病名は　＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

C. その病気でかかっている（かかっていた）病院はどちらですか？
わかる範囲でお答え下さい。

＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿病院

住所＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

電話番号＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

担当医＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿先生

A. いつ頃からですか？　　平成　　年　　月　　頃

B. 病名は　＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

C. その病気でかかっている（かかっていた）病院はどちらですか？
わかる範囲でお答え下さい。

＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿病院

住所＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

電話番号＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

担当医＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿先生

A. いつ頃からですか？　　平成　　年　　月　　頃

B. 病名は　＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

C. その病気でかかっている（かかっていた）病院はどちらですか？
わかる範囲でお答え下さい。

＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿病院

住所＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

電話番号＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

担当医＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿先生

質問６．

アンケート記入は、ご本人が行いましたか？代理の方が行いましたか？○をつけて下さい。

１．ご本人

２．代理の方　→　付問７．へ

付問７．　残念ながら患者さんがお亡くなりになったために、代理の方が記入された場合、下記にお答えください。

A. いつ亡くなられましたか？　平成　　年　　月　　日

B. その原因の病名は（もし、おわかりになればご記入下さい）

＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

C. お亡くなりになった病院はどちらですか？
わかる範囲でお答え下さい。

＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿病院

住所＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

電話番号＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

担当医＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿先生

以上

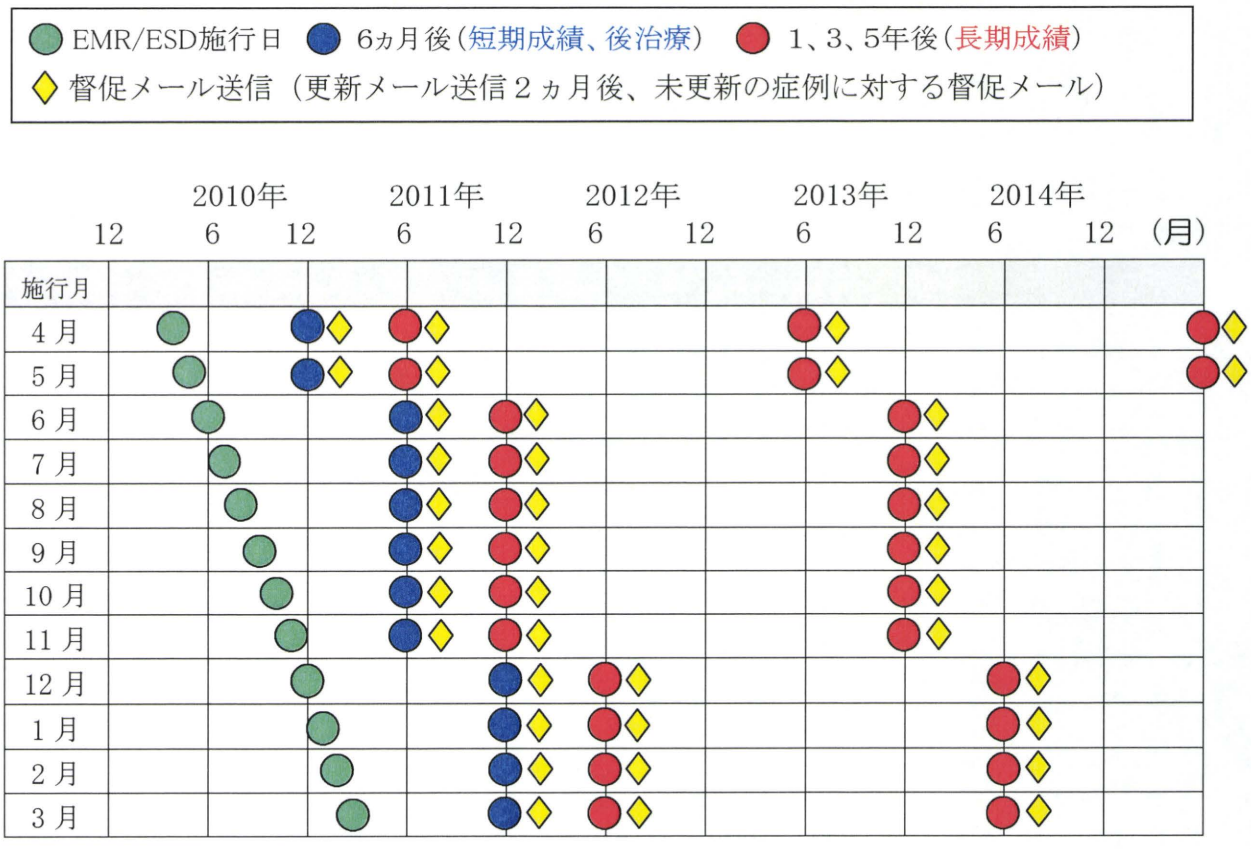
ご協力いただき、有り難うございました。

（資料5）:「自動Eメール送信機能」のシェーマ

内視鏡切除施行より 6 ヶ月後の C. 短期成績、D. 後治療の更新登録、1、3、5 年後の E. 長期成績の更新登録時期を 1 ヶ月以上経過して更新登録されていない症例について、年 2 回（6 月、12 月）各登録施設における登録代表者および当該登録担当医師に対し、更新登録を促す E メールを送信する。

さらに、E メール送信して 2 ヶ月経過しても未更新の症例に対し、再度督促 E メールを送信する。

これらの機能は、サーバ上で自動的・定期的に実行される。



研究成果の刊行に関する一覧表

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Should Elderly Patients Undergo Additional Surgery After Non-Curative Endoscopic Resection for Early Gastric Cancer? Long-Term Comparative Outcomes

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OBJECTIVES: **Endoscopic resection (ER) including endoscopic submucosal dissection has been widely accepted for treatment of early gastric cancer (EGC) in Japan. Additional surgery is recommended when ER is non-curative histologically. Many elderly patients, however, do not undergo radical surgery due to comorbid disease or limited life expectancy. The aim of this study is to assess the survival outcomes of radical surgery compared with observation only in elderly patients after non-curative ER.**

METHODS: **We reviewed existing data of all elderly patients (older than 75 years) who had undergone ER for EGC at the National Cancer Center Hospital between January 1999 and December 2005. We compared the overall and disease-free survival rates between three patients groups: curative ER, non-curative ER with additional surgery, and non-curative ER without additional surgery.**

RESULTS: **In total, 428 patients underwent ER; 308 (72%) curative ER and 120 (28%) non-curative ER. Of the 120 non-curative ER patients, 38 patients (31.7%) underwent additional surgery and 82 patients (68.3%) were followed without surgery. There was no significant difference in American Society of Anesthesiologist score between three groups. Patients who did not undergo surgery tended to be older. Overall 5-year survival rates in the curative ER, non-curative ER with surgery, and non-curative ER without surgery were 85, 92, and 63%, respectively. There was no significant difference in overall and disease-free survival between patients in the curative ER and non-curative ER with surgery groups. On the contrary, a significant difference in overall and disease-free survival was evident between the curative ER and non-curative ER without surgery groups (hazard ratio (95% confidence interval): 1.89 (1.08–3.28), 2.30 (1.35–3.94)).**

CONCLUSIONS: **In our elderly patient cohort, additional surgery following non-curative ER improved overall and disease-free survival compared with non-surgical observation only. Thus, surgery should be considered following non-curative ER in EGC patients >75 years of age.**

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INTRODUCTION

Life expectancy in elderly patients has increased dramatically worldwide (1,2). Although surgical techniques and preoperative management have improved minimally invasive curative treatment is preferable for the elderly, particularly for early stage cancer (EGC).

Endoscopic resection (ER) has been accepted as standard treatment for EGCs that meet guideline or expanded criteria (3,4), which have a low risk of lymph node metastasis. Following ER, meticulous pathological evaluation of the resected specimen is used to stratify patient management. Patients with lesions that meet the guideline or expanded criteria are followed closely, whereas those who have had a non-curative ER are considered for additional surgery.

Gastrectomy is associated with high surgical risk for the general population. Partial or total gastrectomy is also associated with short and long-term morbidity, and mortality (5,6). Furthermore, the majority of elderly patients who are 75 years or older

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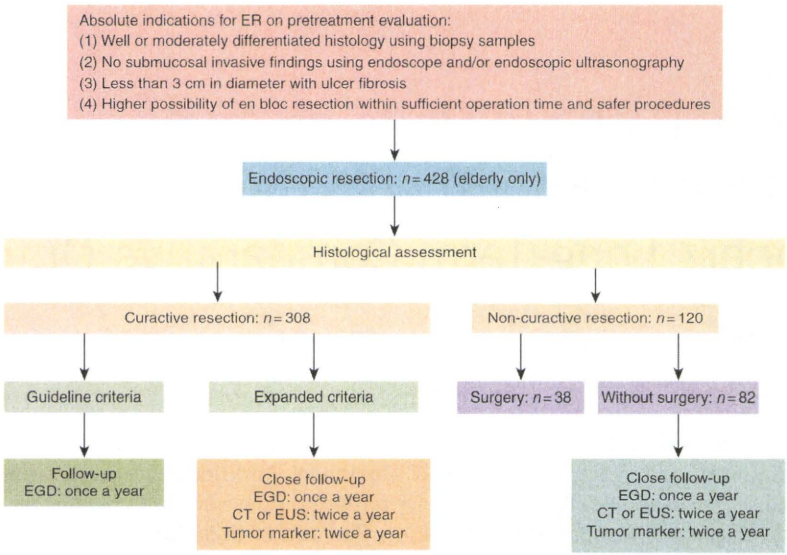

Figure 1. Flowchart of critical procedure. CT, computed tomography; EGD, endogastroduodenoscopy; ER, endoscopic resection; EUS, endoscopic ultrasonography.

have multiple diseases and functional disorders influencing daily life (7,8). In this study, we describe the long-term outcomes of ER for EGC in patients aged 75 years or older. We primarily aim to determine whether lesions beyond the guideline or expanded criteria in this elderly cohort can be treated adequately with ER alone.

METHODS

Study design

We reviewed existing data on all patients who had undergone ER for EGC at the National Cancer Center Hospital, Tokyo, between January 1999 and December 2005. Patients whose lesions did not meet criteria for ER following preoperative diagnosis were excluded. We defined elderly patients as 75 years or older (7). Elderly patients were divided into three groups: curative ER, non-curative ER with additional radical surgery, and non-curative ER without surgery. We used the American Society of Anesthesiologist (ASA) score and Charlson Index (9) as a measurement of patients overall health status, and surgical risk. All patients provided written informed consent.

Method

Starting in 1999, our institution has routinely followed a standard protocol for the ER of EGC.

Indication for ER

Indication criteria for ER—"differentiated histology," "macroscopic absence of submucosal invasive findings using endoscope and/or endoscopic ultrasonography," "lesion size- <3 cm in diameter with ulcer fibrosis," and "high probability of safe en bloc resection with short procedure duration." Patients deemed unfit for open surgery due to their general condition were also judged to be poor candidates for ER (**Figure 1**).

Historical assessment

Resection specimens were classified according to the Japanese Classification for Gastric Carcinoma (10). In this study, ER was declared curative when the specimen showed en bloc resection with margins free of cancer and if applicable, met the expanded criteria: (i) intramucosal cancer, differentiated type, no lymphatic or/and venous invasion, and no ulceration, irrespective of tumor size; (ii) intramucosal cancer, differentiated type, no angiolymphatic invasion, and tumor <3 cm in size, irrespective of ulceration findings; (iii) minimally invasive submucosal cancer (invasion depth $\leq 500\,\mu$m, sm1), differentiated type, no lymphatic or/and venous invasion, and tumor <3 cm in size.

Post ER management

All patients were followed according to our standard protocol (**Figure 1**). Surveillance upper endoscopy was performed annually. Curative cases with expanded criteria also underwent abdominal computed tomography or endoscopic ultrasonography and tumor-marker studies (carcinoembryonic antigen, CA19–9) every 6 months to exclude lymph node or distant metastasis. Patients who underwent non-curative ER and were deemed fit for surgery were referred and consented for radical resection and lymph node dissection. Patients with the non-curative ER without surgery due to physician judgment or strong patient refusal were followed up by the same protocol as patients with curative resection with expanded criteria.

Statistical analysis

Differences in patient characteristics between the three groups were examined by χ^2 test. Survival curves were calculated using the Kaplan–Meier method. To compare overall and disease-free survival among the treatment status, Cox proportional-hazards model was performed to estimate hazard ratio (HR) and 95% confidence interval (CI). The following covariates were included

in the multivariable analyses: age, sex, ASA score, past history of cancer (stratified by cancer stage), and comorbid illnesses. We also compare the overall and disease-free survival in the multivariable analyses included age, sex, and Charlson Index. All P values reported are two-sided, and significance level was set at $P<0.05$. All statistical analyses were performed with the SAS software version 9.1 (SAS Institute Inc., Cary, NC).

RESULTS

Patient characteristics

A total of 2,012 cases (2,399 lesions) of EGC were treated endoscopically at the National Cancer Center Hospital between January 1999 and December 2005. Of these, 1,947 cases (2,331 lesions) met the indication for ER following preoperative diagnosis. In all, 428 (519 lesions) of the 1,947 cases were elderly (75 years or older). Of these cases in elderly patients, 26 lesions were treated by endoscopic mucosal resection and 493 lesions were treated by endoscopic submucosal dissection. A total of 308 elderly patients (72%, 308/428) had a curative ER and 120 patients (28%, 120/428) had a non-curative ER. Of the 120 patients with non-curative ER, 38 patients (31.7%, 38/120) underwent radical surgery and 82 patients (68.3%, 82/120) were followed without surgery.

Patient characteristics are summarized in **Table 1**. ASA score of all patients except nine was 2. In all, 312 patients (72.9%, 312/428) were Charlson Index 2, 65 patients (15.2%, 106/428) were 3, 41 patients (9.6%, 41/428) were 4, and 10 patients were over 5 (2.3%, 10/428). There was no significant difference in ASA score and Charlson Index between three groups (ASA score, $P=0.17$; Charlson Index; $P=0.33$). There was a significant difference in age and the prevalence of cardiovascular disease. Patients who did not undergo surgery tended to be older.

Reasons for not undergoing surgery in the remaining 82 patients included patients' choice ($n=29$), physicians' judgment ($n=45$) (including 10 very elderly (mean age 84 years), one with chronic renal dysfunction, one with ventilatory impairment and one with aneurysm of the thoracic aorta, concomitant cancer in other organs ($n=7$)) and unknown ($n=8$).

Table 1. Patient characteristics

	Curative resection	Non-curative resection with surgery	Non-curative resection without surgery
Number of patients (%)	308 (72.0)	38 (8.9)	82 (19.2)
Age, mean (s.d.)	78.8 (3.3)	76.9 (2.3)	80.1 (3.9)
Gender ratio, men: women	228:80	32:6	67:15
Concomitant disease (%)			
Cancer	59 (19.2)	3 (7.9)	13 (15.9)
Cardiovascular diseases	48 (15.6)	16 (42.1)	11 (13.4)
Diabetes	29 (9.4)	6 (15.8)	7 (8.5)
Respiratory diseases	6 (1.9)	1 (2.6)	3 (3.7)
Other diseases	15 (4.9)	2 (5.3)	6 (7.3)
ASA score (%)			
2	304 (100)	37 (100)	78 (98.7)
3	0	0	1
Missing information	4	1	3
Charlson Index			
2	232 (75.3)	25 (65.8)	55 (67.1)
3	43 (14.0)	8 (21.1)	14 (17.1)
4	25 (8.1)	4 (10.5)	12 (14.6)
5+	8 (2.6)	1 (2.6)	1 (1.2)

ASA, American Society of Anesthesiologist.

Survival

The median follow-up period in the curative ER, non-curative ER with surgery, and non-curative ER without surgery was 40.6, 43.1, and 38.1 months, respectively. Overall 5-year survival in each group was 84, 95, and 63%, respectively (**Table 2**). Using ASA score, age, sex, clinical stage of cancer in past history, and past history of diseases, there was no significant difference in overall and disease-free survival between the patients with curative ER ($n=308$) and non-curative ER with surgery ($n=38$). On the contrary, a significant difference in overall and disease-free survival was evident between the patients with curative ER ($n=308$) and non-curative ER without surgery ($n=82$) (HR (95% CI): 1.89 (1.08–3.28), 2.30 (1.35–3.94); **Table 2**, **Figure 2**). The multivariable analysis using Charlson Index, age, and sex shows a statistical difference in overall and disease-free survival between the patients with curative ER and non-curative ER without surgery (HR (95% CI): overall survival, 2.35 (1.36–4.05); disease-free survival, 2.76 (1.64–4.67)).

In total, 59 patients (13.8%, 54/428) died during this study period. The majority (55.9%, $n=33/59$) of deaths occurred in the curative ER group followed by the non-curative ER without surgery group (40.7%, $n=24/59$). Only two (3.4%) deaths occurred in the group who had non-curative ER with surgery. Of the 428 patients, 1.2% ($n=5$) died as a result of gastric cancer and 12.6% ($n=59/432$) died from another causes (**Table 2**). Of the five patients who died of gastric cancer, one patient died from metachronous advanced gastric cancer following curative ER of the index lesion. Four patients in the non-curative ER without surgery died from lymph node metastasis or distant metastasis. There were no deaths from cancer recurrence in the non-curative ER with surgery.

Survival according to the risk of lymph node metastasis

We divided non-curative ER groups into two groups according to the risk of lymph node metastasis: A—high risk ("positive lymphatic or/and venous invasion" or "submucosal deep (sm2) invasion") and B—low risk (other reasons except high risk of lymph node metastasis such as intramucosal cancer >30 mm in size with ulcer findings and minute submucosal cancer

Table 2. Hazard ratio (HR) and 95% confidence intervals (CIs) of overall survival according to curability

	Number of deaths (death from gastric cancer)	Five-year survival rate (%)	Crude		Multivariable adjusted[a]	
			HR	95% CI	HR	95% CI
Curative ER	33 (1)	84	1.00		1.00	
Non-curative ER with surgery	2 (0)	95	0.52	0.13–2.17	0.70	0.16–2.98
Non-curative ER without surgery	24 (4)	63	2.62	1.54–4.46	1.89	1.08–3.28

ASA, American Society of Anesthesiologist; ER, endoscopic resection.
[a]Adjusted for age, sex, ASA score, clinical stage of cancer in past history, and past history of diseases (cardiovascular diseases, diabetes mellitus, respiratory diseases, and others).

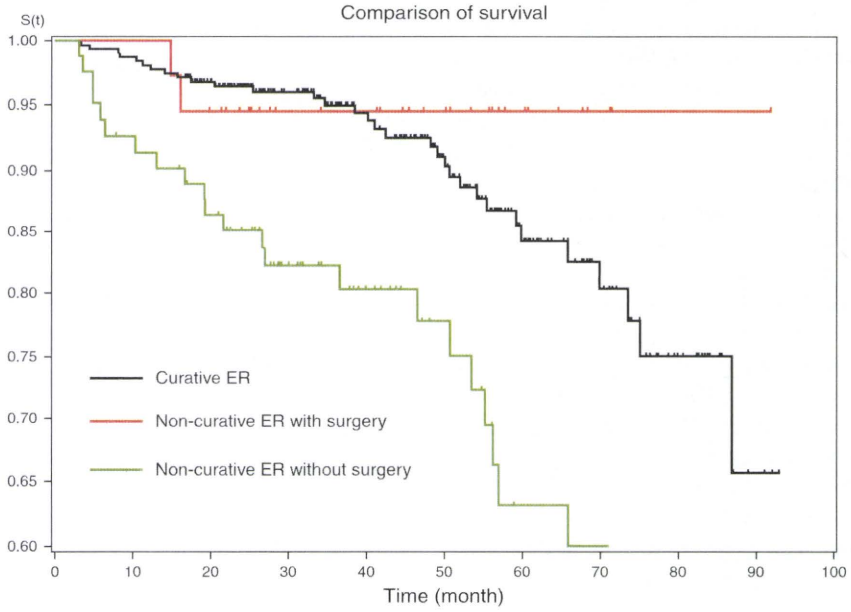

Figure 2. Survival for elderly patients (overall survival). ER, endoscopic resection.

(sm1) >30 mm in size). Among the non-curative ER patients, 29 of the 67 high-risk patients (43.3%) underwent additional surgery compared with only 9 patients of the 53 low-risk patients (17.0%). **Table 3** shows overall survival according to the risk of lymph node metastasis using ASA score, age, sex, clinical stage of cancer in past history, and past history of diseases. Overall 5-year survival rate in non-curative ER-A without surgery group was lowest (52%). There were significant difference in overall and disease-free survival between the patients with curative ER (n=308) and non-curative ER-A without surgery group (HR (95% CI): 3.31 (1.67–6.58), 4.26 (2.20–3.94); **Table 3**). In the multivariable analysis using Charlson Index, age, and sex, a statistical significance was evident in overall and disease-free survival between the patients with curative ER and non-curative ER-A without surgery (HR (95% CI): overall survival, 4.15 (2.18–7.89); disease-free survival, 5.30 (2.85–9.84)).

DISCUSSION

Surgery continues to be the mainstay of treatment for gastric cancer—with a reported high resection rate (96%) and a low surgical complication rate (8%) even in elderly patients (11). However, 5-year survival after surgery in elderly patients varies among institutions, and is reported to be 69–74% for EGC. This is compared with 5-year survival rates of >90% in young and middle-aged patients (12). Age-related disease, in fact, is the main etiology of the relatively low survival in elderly patients. Thus, less invasive surgical treatment is desirable in the elderly, and ER is attractive in this respect.

ER targets EGC lesions that have a negligible likelihood of lymph node metastasis, estimated at <1% for intramucosal cancer and <3% for submucosal invasive cancer (4). Several recent studies have reported that endoscopic submucosal dissection can be carried out on larger lesions resulting in a high rate of cancer-free

Table 3. Hazard ratio (HR) and 95% confidence intervals (CIs) of overall survival according to the risk of lymph node metastasis

	Number of subject	Number of deaths (death from gastric cancer)	Five-year survival rate (%)	Crude		Multivariable adjusted[a]	
				HR	95% CI	HR	95% CI
Curative ER	308	33	84	1.00		1.00	
Non-curative ER-A with surgery	29	1 (0)	96	0.36	0.05–2.66	0.54	0.07–4.07
Non-curative ER-B with surgery	9	1 (0)	89	0.96	0.13–7.01	1.09	0.15–8.14
Non-curative ER-A without surgery	38	14 (3)	52	4.72	2.52–8.85	3.31	1.67–6.58
Non-curative ER-B without surgery	44	10 (1)	71	1.55	0.75–3.22	1.17	0.56–2.47

ASA, American Society of Anesthesiologist; ER, endoscopic resection.
[a]Adjusted for age, sex, ASA score, clinical stage of cancer in past history, and past history of diseases (cardiovascular diseases, diabetes mellitus, respiratory diseases, and others).

margin (13,14). Long-term survival of EGC patients undergoing ER with expanded criteria has been equal to those undergoing ER with original guidelines (15). Expanded criteria for ER of larger tumors may benefit elderly patients with EGC (16).

As a general rule, additional surgery should be recommended for patients when curative ER is not achieved (17), as EGC surgical outcomes are known to be excellent (11). Our study provides long-term survival data of EGC in an elderly cohort. We demonstrate the efficacy of curative ER for EGC, showing a similar 5-year survival rate among elderly patients with curative ER and non-curative ER with surgery. We found that when curative ER was not achieved, elderly patients appeared to benefit from subsequent surgical gastrectomy. Furthermore, patients who had a non-curative ER without surgery and were established to have a high risk of lymph node metastasis had the lowest overall 5-year survival rate of 52%.

It was reported that lymphovascular involvement and massive submucosal penetration had a significant association with lymph node metastasis in EGC (18). From our data, there were significant difference in overall and disease-free survival between the patients with curative ER and non-curative ER-A without surgery group. Lymphovascular involvement or massive submucosal penetration was more frequent in surgical patients than in non-surgical patients. It is likely that the physician suggested additional surgery to these patients with high risk of lymph node metastasis. Considering the patient's age and the risk of lymph node metastasis in this recommendation.

Notably, the patients with the non-curative ER without surgery did not undergo additional surgery primarily due to subjective measures. Thus, although the treating physician routinely discussed and recommended radical surgery to all patients with non-curative ER, individual factors such as comorbid disease, reason for non-curative ER, age, and patient preference ultimately influenced treatment decisions. These conditions are subjective and cannot be expressed numerically, and are an inherent limitation of our retrospective study.

In conclusion, following non-curative ER for ECG, especially with lymphovascular involvement or massive submucosal penetration, additional surgery is recommended in elderly patients.

CONFLICT OF INTEREST

Guarantor of the article: Chika Kusano, MD, PhD.

Specific author contributions: Conceptualization, data analysis, and script preparation: Chika Kusano and Motoki Iwasaki; endoscopic diagnosis and treatment: Takuji Gotoda and Ichiro Oda; data collection: Chika Kusano, Ichiro Oda, and Takuji Gotoda; critical reviewer of the paper: Ichiro Oda, Takuji Gotoda, Tonya Kaltenbach, and Abby Conlin. All authors have read and approved the submitted version of the paper.

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Potential competing interests: None.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Endoscopic resection (ER) has been accepted as standard treatment for early gastric cancers, which have a low risk of lymph node metastasis.
- ✓ Additional surgery with lymph node dissection should be recommended for patients when curative ER is not achieved.
- ✓ Deciding whether or not to pursue gastric surgery or not is particularly complex in elderly patients who often have comorbidities and limited life expectancy.

WHAT IS NEW HERE

- ✓ A significant difference in overall and disease-free survival was evident between the patients with curative endoscopic resection (ER) and non-curative ER without surgery (hazard ratio (95% confidence interval): 1.89 (1.08–3.28), 2.30 (1.35–3.94)).
- ✓ Overall and disease-free survival of non-curative ER with "positive lymphatic or/and venous invasion" or "submucosal deep (sm2) invasion" are lowest.
- ✓ After non-curative ER for early gastric cancer, especially with lymphovascular involvement or massive submucosal penetration in historical findings, additional surgery is necessarily even in elderly patients.

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ORIGINAL ARTICLE

Correlation between endoscopic macroscopic type and invasion depth for early esophagogastric junction adenocarcinomas

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Abstract
Background Although correlations between endoscopic macroscopic type and tumor depth have been reported for superficial esophageal squamous cell carcinoma and early gastric and early colorectal adenocarcinomas, there is no published study investigating the correlation between endoscopic macroscopic type and invasion depth for mucosal (M) and submucosal (SM) adenocarcinomas located at the esophagogastric junction (EGJ). We decided to analyze, therefore, the relationship between endoscopic macroscopic type and tumor depth for such cancers.
Methods We retrospectively reviewed 73 early EGJ adenocarcinomas (M/SM = 33/40; differentiated/undifferentiated type = 70/3) in 73 consecutive patients treated endoscopically and/or surgically between January 2000 and December 2008. The mean age of the patients was 63.9 years (range 37–85 years) and the male/female ratio was 62:11. EGJ adenocarcinoma was defined as junctional carcinoma (type II) according to the Siewert classification.
Results We found polypoid type lesions (0-I) in 14 patients, non-polypoid type without mixed type (0-IIa, 0-IIb, or 0-IIc) in 39, and mixed type (0-IIa + IIc or 0-IIc + IIa) in 20 patients. Non-polypoid type without mixed type (31%; 12/39) lesions had a significantly lower risk for SM invasion compared to polypoid type (79%; 11/14; $p < 0.01$) and mixed type (85%; 17/20; $p < 0.01$) lesions. In polypoid type lesions, the risk of SM invasion was significantly lower for the pedunculated subtype (0-Ip) than for the sessile subtype (0-Is) lesions (0%; 0/2 vs. 92%; 11/12; $p < 0.05$). M lesions (mean size 14.5 ± 7.5 mm) were significantly smaller than SM lesions (24.5 ± 7.7 mm; $p < 0.01$).
Conclusions Determination of endoscopic macroscopic type may be useful in accurately diagnosing early EGJ adenocarcinoma invasion depth.

Keywords Esophagogastric junction · Adenocarcinoma · Endoscopic macroscopic type · Depth of invasion

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Introduction

Accurate endoscopic diagnosis of invasion depth for gastrointestinal cancer is essential for making the proper decision on treatment strategy. The use of endoscopic resection in treating early gastrointestinal cancer has become more widespread recently. As a result, the differential endoscopic diagnosis of mucosal (M) and submucosal (SM) depth of invasion has become increasingly important for determining the indications for endoscopic resection [1–3].

Endoscopy examination is the primary modality for diagnosing gastrointestinal cancer and is also helpful in diagnosing invasion depth. Correlations between endoscopic macroscopic type and invasion depth have been

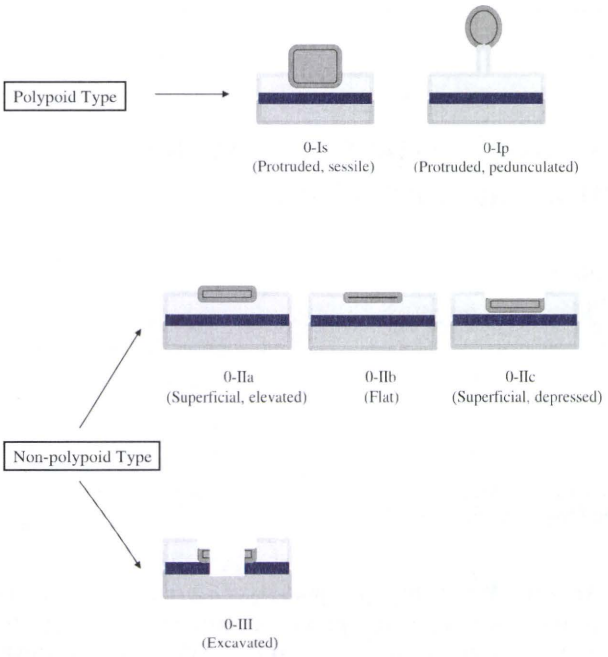

Fig. 1 Classification of endoscopic macroscopic types of early esophagogastric junction adenocarcinomas

reported for superficial esophageal squamous cell carcinoma and early gastric and early colorectal adenocarcinomas in *The Paris endoscopic classification of superficial neoplastic lesions* [4], and in an even more recent evaluation, of endoscopic macroscopic types in early Barrett's neoplasia, such correlations have also been reported [5]. There has been no previously published study, however, investigating the correlation between endoscopic macroscopic type and invasion depth for M and SM adenocarcinomas located at the esophagogastric junction (EGJ). The intention of this study was to clarify the relationship between endoscopic macroscopic type and invasion depth for such early EGJ adenocarcinomas.

Patients and methods

A total of 73 early EGJ adenocarcinomas in 73 consecutive patients treated endoscopically and/or surgically between January 2000 and December 2008 at the National Cancer Center Hospital in Tokyo, Japan, were retrospectively analyzed in this study. EGJ adenocarcinoma was defined as a junctional carcinoma (type II) according to the Siewert classification [6]. An upper gastrointestinal endoscopy examination was performed on each patient before treatment.

We reviewed the clinical records and endoscopic and pathological reports for every patient and analyzed the relationships between invasion depth of early EGJ adenocarcinomas and the following clinicopathological findings: age, gender, initial treatment, histological type, histological findings with regard to a diagnosis of Barrett's cancer, center of tumor location, tumor size, and endoscopic macroscopic type.

Table 1 Clinicopathological findings of 73 patients with esophagogastric junction adenocarcinoma

Age, mean ± SD (years)	63.9 ± 12.0
Sex (%)	
Male	62 (85)
Female	11 (15)
Invasion depth (%)	
Mucosal	33 (45)
Submucosal	40 (55)
Initial treatment (%)	
Endoscopic resection	40 (55)
Surgical resection	33 (45)
Histological type (%)	
Differentiated type	70 (96)
Undifferentiated type	3 (4)
Histological finding (%)	
Barrett's cancer	42 (58)
Non-Barrett's cancer	31 (42)
Tumor location, quarter (%)	
12:01–3 o'clock	50 (68)
3:01–6 o'clock	10 (14)
6:01–9 o'clock	3 (4)
9:01–12 o'clock	10 (14)
Tumor size, mean ± SD (mm)	20.0 ± 9.1
Endoscopic macroscopic type (%)	
0-I	14 (19)
0-IIa	8 (11)
0-IIb	1 (1)
0-IIc	30 (41)
0-IIa + IIc	17 (23)
0-IIc + IIa	3 (4)
0-III	0 (0)

SD Standard deviation

Invasion depth for early EGJ adenocarcinomas was divided into M and SM and initial treatment was divided into endoscopic resection and surgical resection. Histological type was diagnosed based on the predominant tumor pattern in the M layer and then divided into two types: differentiated type and undifferentiated type, according to the *Japanese classification of gastric carcinoma* [7]. The histological findings with regard to a diagnosis of Barrett's cancer were classified as Barrett's cancer and non-Barrett's cancer, with Barrett's cancer diagnosed whenever a tumor was continuously located on Barrett's esophagus. The center of tumor location was divided into quarters (12:01–3:00, 3:01–6:00, 6:01–9:00, and 9:01–12:00 o'clock), using

Table 2 Correlation between clinicopathological findings and invasion depth

	Invasion depth		*p* value
	Mucosal ($n = 33$)	Submucosal ($n = 40$)	
Age, mean ± SD (years)	63.3 ± 11.5	64.3 ± 12.5	NS
Sex (%)			
Male	28 (45)	34 (55)	NS
Female	5 (45)	6 (55)	
Histological type (%)			
Differentiated type	33 (47)	37 (53)	NS
Undifferentiated type	0 (0)	3 (100)	
Histological findings (%)			
Barrett's cancer	23 (55)	19 (45)	NS
Non-Barrett's cancer	10 (32)	21 (68)	
Tumor location, half (%)			
12:01–6 o'clock	28 (47)	32 (53)	NS
6:01–12 o'clock	5 (38)	8 (62)	
Tumor size, mean ± SD (mm)	14.5 ± 7.5	24.5 ± 7.7	<0.01
Endoscopic macroscopic type (%)			
Polypoid type (0-I)	3 (21)	11 (79)	<0.01*
Non-polypoid type without mixed type (0-IIa, 0-IIb or 0-IIc)	27 (69)	12 (31)	
Mixed type (0-IIa + IIc or 0-IIc + IIa)	3 (15)	17 (85)	<0.01*

SD Standard deviation, *NS* not significant

* Significantly different from non-polypoid type without mixed type

the forward endoscopic EGJ view. Tumor size was defined as the length of the major axis. Endoscopic macroscopic type was classified based on the Paris classification and divided into polypoid (0-I) and non-polypoid (0-IIa, 0-IIb, 0-IIc and 0-III) types (Fig. 1) [4]. A mixed type was diagnosed whenever a lesion consisted of at least two distinct endoscopic macroscopic types. Polypoid type lesions were then subdivided into sessile (0-Is) and pedunculated (0-Ip) subtype lesions.

Data were analyzed using the χ^2 test, Fisher's exact test, or Student's t test as appropriate. Value differences in which $p < 0.05$ were considered statistically significant.

Results

Clinicopathological findings are shown in Table 1. The mean age ± standard deviation (SD) of the patients was 63.9 ± 12.0 years and the male/female ratio was 5.64 (62:11). Relationships between clinicopathological findings and invasion depth are shown in Table 2. M lesions (mean size 14.5 ± 7.5 mm) were significantly smaller than SM lesions (24.5 ± 7.7 mm; $p < 0.01$). Non-polypoid type without mixed type (0-IIa, 0-IIb or 0-IIc) lesions had a significantly lower risk for SM invasion than polypoid type (0-I) and mixed type (0-IIa + IIc or 0-IIc + IIa) lesions (Table 2; see images in Figs. 2, 3, 4). When polypoid type lesions were subdivided into sessile (0-Is) and pedunculated (0-Ip) subtypes, the risk of SM invasion was significantly lower for the pedunculated subtype than for the sessile subtype (0%; 0/2 vs. 92%, 11/12; $p < 0.05$) (see images in Figs. 4, 5).

Discussion

There has been a dramatic increase in the incidence of EGJ adenocarcinomas in the United States and other Western countries over the past two decades [8–12]. It has also been reported from a large referral center in Japan that the proportion of EGJ adenocarcinomas among all gastric adenocarcinomas detected in Japanese patients has been increasing in recent years [13].

Remarkable progress has been made during the past decade in the development and refinement of endoscopic resection methods, from conventional endoscopic mucosal resection (EMR) to endoscopic submucosal dissection (ESD) [14–20], which has been applied to early EGJ adenocarcinomas [21]. Consequently, accurate differential endoscopic diagnosis of M and SM invasion depth in early EGJ adenocarcinomas has become more important for determining the indications for such procedures.

Endoscopic ultrasonography (EUS) is one of the current modalities used for diagnosing tumor invasion depth. Using conventional EUS (7.5 MHz), advanced T3/T4 carcinomas can be distinguished from T1/T2 carcinomas in

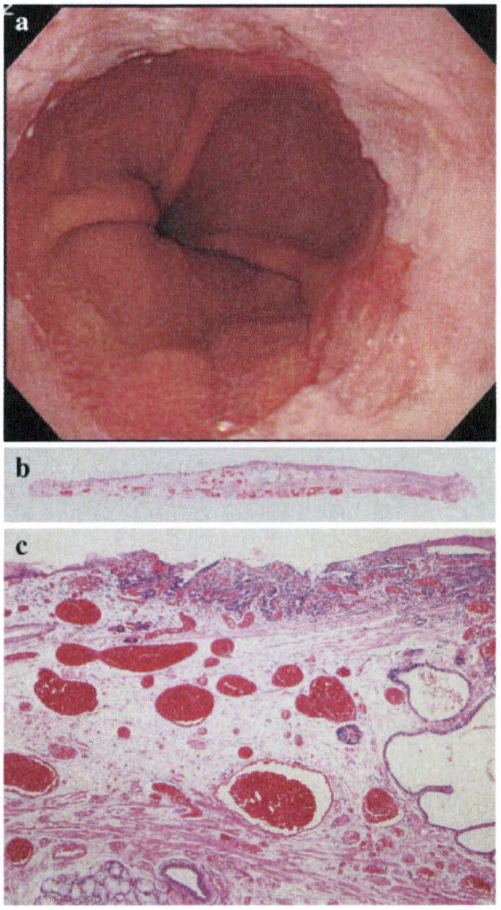

Fig. 2 **a** Endoscopic image reveals a non-polypoid type without mixed type, slightly depressed (0-IIc) lesion at the esophagogastric junction (EGJ). **b**, **c** Histological features of the resected specimen indicate a well-differentiated adenocarcinoma confined to the mucosal layer that had spread to the subepithelial layer of the esophagus (**b** H&E, panoramic view), (**c** H&E, ×40)

more than 80% of cases; however, accurate differentiation between M and SM invasion depth is difficult [22–24]. EUS using a miniprobe (20 MHz) has reportedly demonstrated a high diagnostic accuracy of approximately 80% for differentiating between M and SM early EGJ adenocarcinomas. There was no significant difference, however, between EUS diagnostic accuracy and that of high-resolution video endoscopy [23]. Consequently, endoscopy can also be helpful in diagnosing invasion depth, but such diagnosis is subjective in nature so there is a need for objective criteria.

In the present study, we analyzed the relationship between the invasion depth of early EGJ adenocarcinomas and relevant clinicopathological findings, including endoscopic macroscopic type. We found that M lesions were

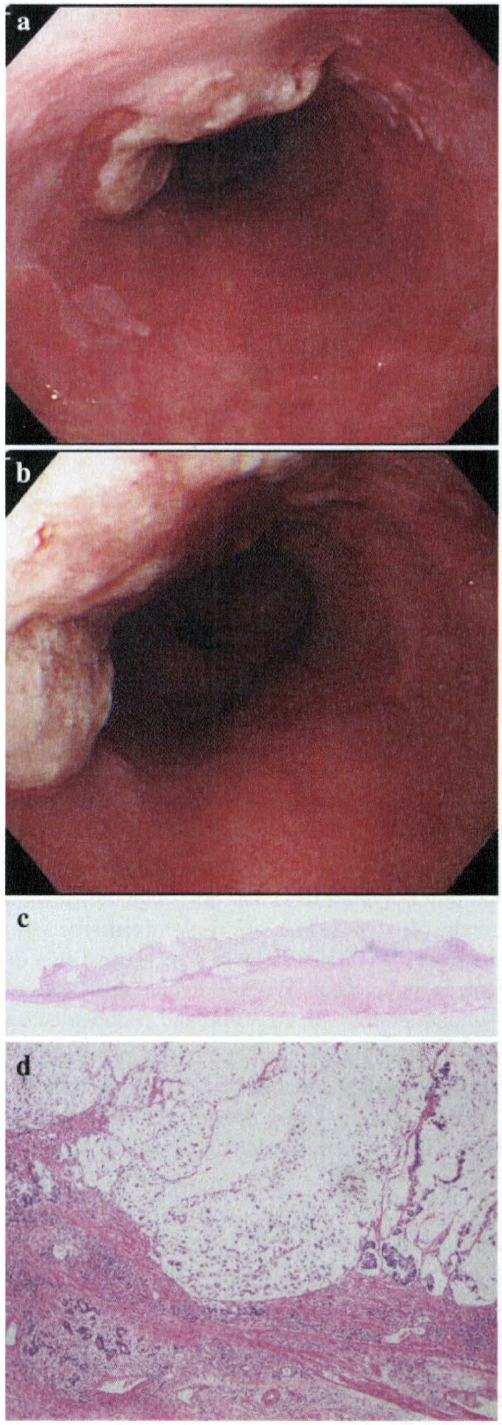

Fig. 3 **a**, **b** Endoscopic images reveal a mixed type, elevated lesion with a central depression (0-IIa + IIc) at the EGJ. **c**, **d** Histological features of the resected specimen indicate a mucinous adenocarcinoma in the mucosal layer and a poorly differentiated adenocarcinoma that had invaded the submucosal layer (**c** H&E, panoramic view), (**d** H&E, ×100)

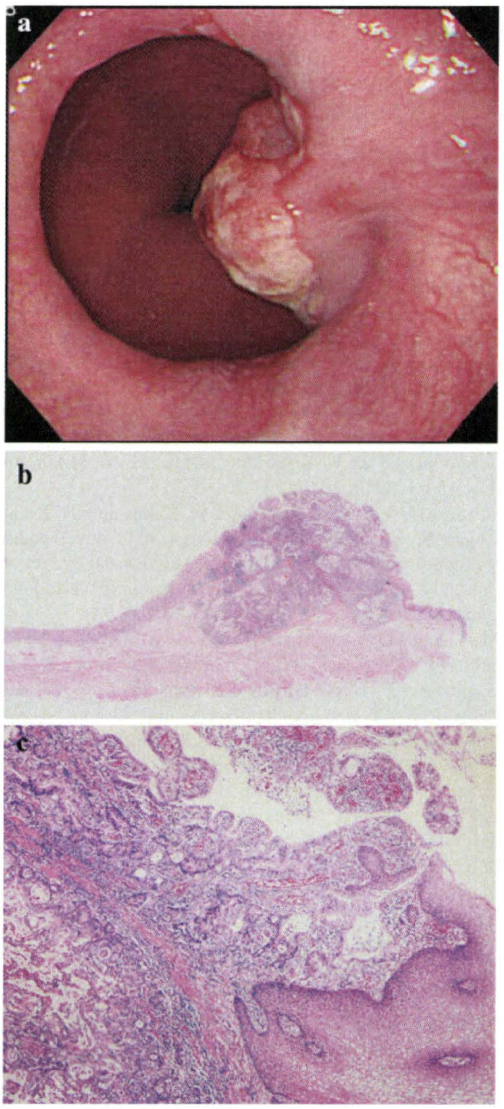

Fig. 4 **a** Endoscopic image reveals a polypoid type, sessile subtype (0-Is) lesion at the EGJ. **b**, **c** Histological features of the resected specimen indicate a well-differentiated adenocarcinoma that had invaded the submucosal layer (**b** H&E, panoramic view), (**c** H&E, ×100)

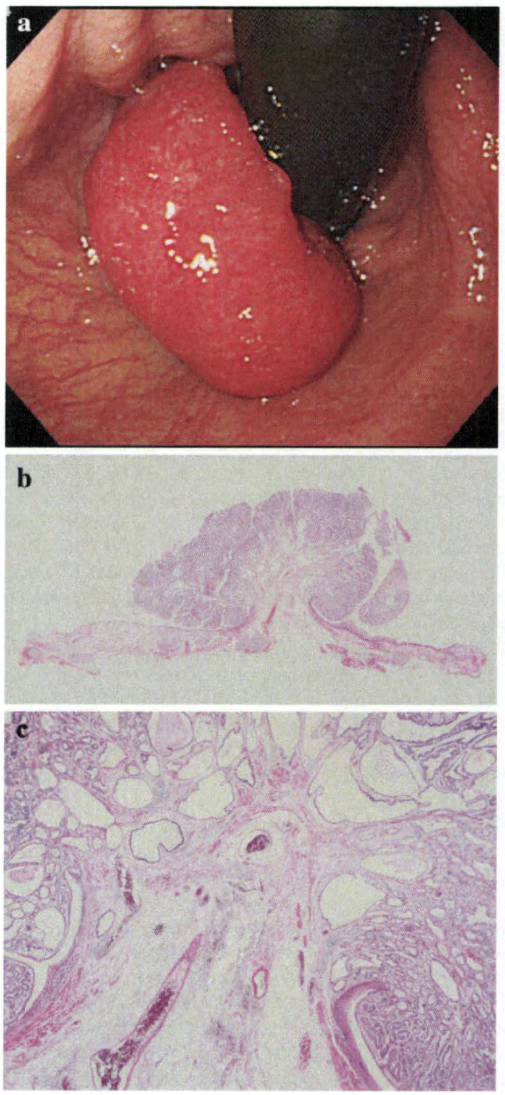

Fig. 5 **a** Endoscopic image reveals a polypoid type, pedunculated subtype (0-Ip) lesion at the EGJ. **b**, **c** Histological features of the resected specimen indicate a well-differentiated adenocarcinoma confined to the mucosal layer (**b** H&E, panoramic view), (**c** H&E, ×100)

significantly smaller than SM lesions. Non-polypoid type without mixed type (0-IIa, 0-IIb or 0-IIc) lesions had a significantly lower risk for SM invasion compared to polypoid type (0-I) and mixed type (0-IIa + IIc or 0-IIc + IIa) lesions. In the polypoid type lesions, the risk for SM invasion was significantly lower for the pedunculated subtype (0-Ip) than for the sessile subtype (0-Is) lesions. These results were similar to those in previously published reports of other gastrointestinal neoplasias [4, 5].

One limitation of the present study is that it was a retrospective investigation from a single center, with a relatively small number of reported cases, so a large prospective study will be needed to confirm our findings on the correlation of endoscopic macroscopic type with invasion depth for early EGJ adenocarcinomas. Another limitation of our study was that invasion depth for early EGJ adenocarcinomas was divided into M and SM, but SM was not further subdivided into SM1 and SM2, because the definition of SM1 for EGJ adenocarcinomas is still undecided at the present time. SM1 for gastric cancer and esophageal cancer is defined as a tumor that invades less than 500 μm and less than 200 μm, respectively, into the submucosa from the muscularis mucosa and is associated with a lower

risk of lymph-node metastasis compared with SM2 [4]. Additional investigation as to an accurate definition of SM1 and the risk of lymph-node metastasis for EGJ adenocarcinomas is also necessary.

In conclusion, this retrospective study demonstrated that there were certain correlations between endoscopic macroscopic type and invasion depth for early EGJ adenocarcinomas. As a result, determination of endoscopic macroscopic type may be useful in accurately diagnosing invasion depth for EGJ adenocarcinomas.

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