Original article

# Effect of rescue surgery after non-curative endoscopic resection of early gastric cancer

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**Background:** **Whether rescue surgery confers a survival benefit in patients undergoing non-curative endoscopic resection of early gastric cancer remains controversial.**

**Methods:** **This was a retrospective review of patients who underwent non-curative endoscopic resection of at least one lesion of differentiated-type early gastric cancer between 2000 and 2011. Patients with a positive lateral resection margin as the only non-curative factor were excluded. Outcome was investigated by univariable (Kaplan–Meier) and multivariable (Cox proportional hazards) analysis.**

**Results:** **Some 341 patients underwent non-curative endoscopic resection for at least one lesion of differentiated-type early gastric cancer. Sixty-seven patients with a positive lateral resection margin as the only non-curative factor were excluded, leaving 274 patients for analysis; 194 had rescue surgery and 80 had no additional treatment. The median duration of follow-up was 60·5 months. Patients who had rescue surgery were younger, had a lower Charlson co-morbidity index score, smaller tumours and a higher lymphovascular invasion rate than patients with no treatment. Among 194 patients who had rescue surgery, intragastric local residual tumours were found in ten (5·2 per cent) and lymph node metastases in 11 (5·7 per cent). Patients with lymph node metastasis were significantly older than those without metastasis; no other significant differences were found. Univariable analysis showed that patients aged less than 65 years, those with a Charlson co-morbidity index score below 4 and patients undergoing rescue surgery had significantly longer overall survival. Five-year overall survival rates in the rescue surgery and no-treatment groups were 94·3 and 85 per cent respectively. In multivariable analysis, rescue surgery was identified as the only independent predictor of overall survival after non-curative endoscopic resection of early gastric cancer.**

**Conclusion:** **Rescue surgery confers a survival benefit after non-curative endoscopic resection of early gastric cancer.**

Paper accepted 15 May 2015
Published online 27 August 2015 in Wiley Online Library (www.bjs.co.uk). **DOI:** 10.1002/bjs.9873

## Introduction

Endoscopic resection is currently accepted as a curative treatment for early gastric cancers meeting absolute or expanded indications, as these tumours have a negligible risk of lymph node metastasis[1–3]. However, endoscopic prediction of early gastric cancer in terms of tumour size or depth is not always accurate, even when endoscopic ultrasonography is used[4,5]. Therefore, some patients undergo non-curative endoscopic resection and have a considerable risk of lymph node metastasis on pathological review of the resection specimen. Non-curative procedures are reported to account for 15·3–16·7 per cent of all endoscopic resections for early gastric cancer[6,7].

Additional radical gastrectomy with lymph node dissection is generally recommended in patients who have undergone non-curative endoscopic resection of early gastric cancer because of fear of lymph node metastasis and the possibility of an unfavourable prognosis[1,2]. However, other factors such as age or co-morbidity can also affect survival. In addition, progression from early to advanced gastric cancer occurs in only a limited proportion of patients. Substantial time is usually required for progression from early to advanced gastric cancer, reflecting the slow growth[8,9]. These factors might limit the effect of rescue surgery on the prognosis after non-curative endoscopic resection of early gastric cancer.

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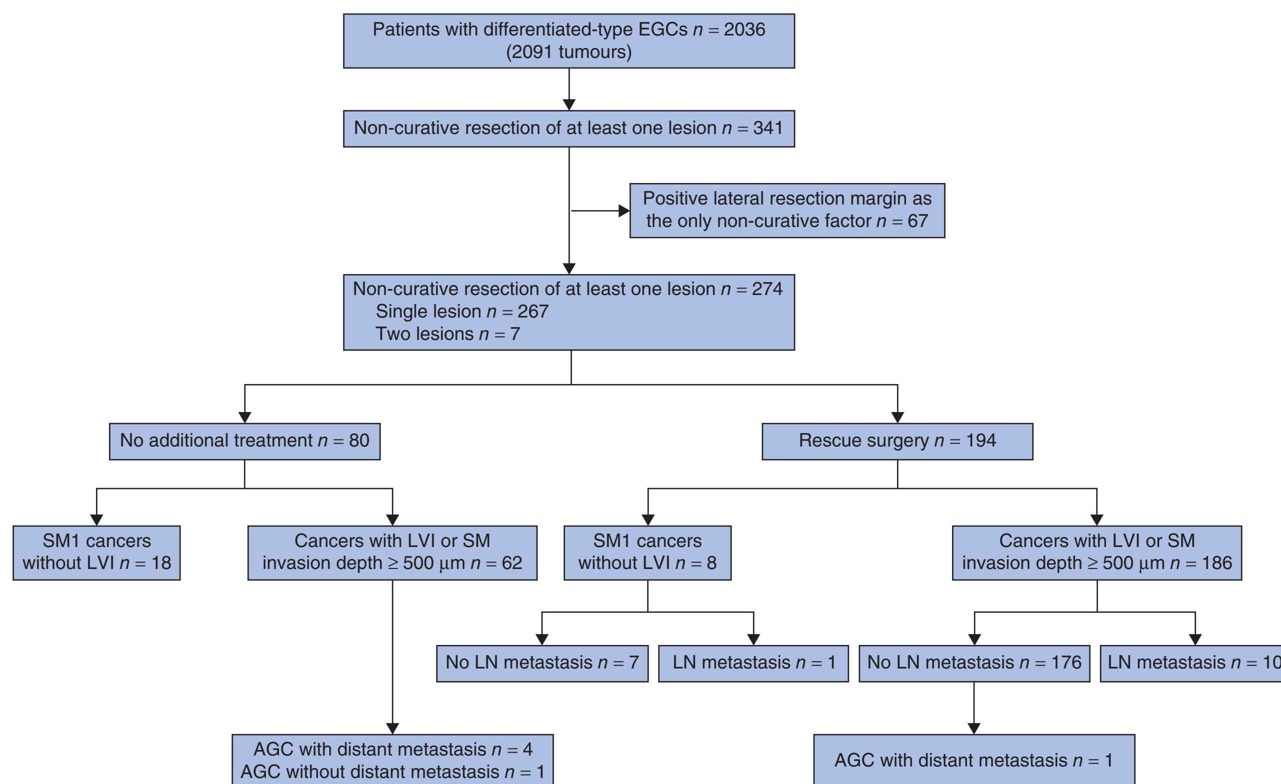


**Fig. 1** Flow chart of enrolled patients undergoing non-curative endoscopic resection of early gastric cancer (EGC). SM1, submucosal tumour invasion depth less than 500 µm from muscularis mucosa layer; LVI, lymphovascular invasion; SM, submucosal; LN, lymph node; AGC, advanced gastric cancer

Only a few studies have assessed the survival benefit of rescue surgery after non-curative endoscopic resection of early gastric cancer, and the results are conflicting. In one study[7], 5-year survival rates were comparable for patients who did and did not have rescue surgery (97·8 and 91 per cent respectively). In another study[10], which included only elderly patients aged over 75 years, the 5-year survival rate of patients undergoing rescue surgery after non-curative endoscopic resection of early gastric cancer was 95 per cent, compared with only 63 per cent among those who did not receive additional treatment.

The present study investigated whether rescue surgery confers a survival benefit in patients undergoing non-curative endoscopic resection of early gastric cancer.

## Methods

This was a retrospective review of patients who underwent their first endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) for at least one lesion of differentiated-type early gastric cancer (well or moderately differentiated early gastric cancer or papillary early gastric cancer) at Samsung Medical Centre between 2000 and 2011. The study protocol was approved by the institutional review board at Samsung Medical Centre. At this institution, endoscopic resection is not indicated for poorly differentiated or signet ring cell early gastric cancer, and patients with these types were excluded from the study. The resection was judged as curative when all of the following conditions were fulfilled: well or moderately differentiated early gastric cancer, or papillary early gastric cancer; *en bloc* or piecemeal resection with successful reconstruction; negative lateral resection margins; negative vertical resection margin; and no lymphovascular invasion. The following size and depth criteria also applied: tumour 2 cm or smaller, mucosal cancer, no ulcer in tumour (early gastric cancer meeting absolute indication); tumour larger than 2 cm, mucosal cancer, no ulcer in tumour; tumour 3 cm or smaller, mucosal cancer, ulcer in tumour; or tumour 3 cm or smaller, SM1 cancer (submucosal invasion depth less than 500 µm from muscularis mucosa layer)[3]. In this institution, radical gastrectomy with D2 lymph node dissection is generally recommended after non-curative endoscopic resection, except in patients with a positive

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**Table 1** Comparison of clinicopathological characteristics of patients who had rescue surgery or no additional treatment after non-curative endoscopic resection for differentiated-type early gastric cancer

| | No additional treatment ($n = 80$) | Rescue surgery ($n = 194$) | $P$* |
|---|---|---|---|
| Age (years) | | | < 0·001† |
| Mean(s.d.) | 67·6(10·6) | 62·7(8·5) | |
| Median (range) | 69·4 (42–86) | 63·1 (44–84) | |
| Sex ratio (M : F) | 55 : 25 | 150 : 44 | 0·137 |
| Concomitant disease | | | |
| Cancer | 9 (11) | 15 (7·7) | 0·349 |
| Cardiovascular disease | 44 (55) | 75 (38·7) | 0·013 |
| Respiratory disease | 5 (6) | 11 (5·7) | 0·785‡ |
| Diabetes | 15 (19) | 33 (17·0) | 0·731 |
| Charlson co-morbidity index score | | | 0·001† |
| Mean(s.d.) | 4·1(2·2) | 3·2(1·3) | |
| Median (range) | 4 (1–11) | 3 (1–8) | |
| Procedure | | | 1·000 |
| Endoscopic submucosal dissection | 76 (95) | 183 (94·3) | |
| Endoscopic mucosal resection | 4 (5) | 11 (5·7) | |
| Resection | | | 0·690 |
| *En bloc* | 74 (93) | 182 (93·8) | |
| Piecemeal | 6 (7) | 12 (6·2) | |
| Tumour site | | | 0·185 |
| Antrum, angle | 46 (58) | 128 (66·0) | |
| Body, fundus, cardia | 34 (42) | 66 (34·0) | |
| Mean(s.d.) tumour size (cm) | 2·7(1·6) | 2·1(1·1) | 0·002† |
| Tumour depth | | | 0·258§ |
| Mucosa | 2 (3) | 19 (9·8) | |
| SM1 | 24 (30) | 31 (16·0) | |
| SM invasion depth ≥ 500 μm | 54 (68) | 144 (74·2) | |
| Differentiation | | | 0·186 |
| Well differentiated | 21 (26) | 37 (19·1) | |
| Moderately differentiated | 59 (74) | 157 (80·9) | |
| Lateral resection margin | | | 0·355 |
| Negative | 75 (94) | 174 (89·7) | |
| Positive | 4 (5) | 19 (9·8) | |
| Unknown | 1 (1) | 1 (0·5) | |
| Vertical resection margin | | | 0·922 |
| Negative | 66 (83) | 161 (83·0) | |
| Positive | 14 (18) | 33 (17·0) | |
| Unknown | 0 (0) | 0 (0) | |
| Lymphovascular invasion | | | < 0·001 |
| No | 57 (71·3) | 81 (41·8) | |
| Yes | 23 (28·8) | 113 (58·2) | |

Values in parentheses are percentages unless indicated otherwise. SM1, submucosal invasion depth less than 500 μm from muscularis mucosa layer; SM, submucosal. *$\chi^2$ test, except †Student's $t$ test and ‡Fisher's exact test. §Mucosa or SM1 *versus* SM invasion depth of 500 μm or more.

lateral resection margin as the only non-curative factor. In the latter patients, additional endoscopic treatment such as ESD is usually recommended. To date, no study has reported lymph node metastasis in patients with a positive lateral resection margin as the only non-curative factor if they underwent additional endoscopic treatment[3,7,11].

## Endoscopic resection techniques

The EMR and ESD procedures have been described in detail elsewhere[12]. In brief, ESD consists of three steps: injecting fluid into the submucosal layer to separate it from the proper muscle layer; circumferential precutting of the mucosa surrounding the lesion; and submucosal dissection of the connective tissue under the lesion with an electrosurgical knife. In the EMR procedure, a snare is used for resection instead of an electrosurgical knife. Circumferential precutting is undertaken in EMR with circumferential precutting, but not in strip biopsy, EMR using a cap or EMR with ligation. All enrolled patients provided written informed consent before undergoing EMR or ESD.

## Histopathological evaluation

Endoscopic resection specimens were stretched, pinned to a polystyrene plate, and immersed in 10 per cent

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**Table 2** Comparison of clinicopathological characteristics according to the presence of lymph node metastasis among patients undergoing rescue surgery

| | No LN metastasis (*n* = 183) | LN metastasis (*n* = 11) | *P** |
|---|---|---|---|
| Age (years) | | | 0·019† |
| Mean(s.d.) | 62·4(8·4) | 68·6(8·7) | |
| Median (range) | 63·0 (44–84) | 68·1 (57–80) | |
| Sex ratio (M : F) | 142 : 41 | 8 : 3 | 0·715 |
| Tumour site | | | 0·338 |
| Antrum, angle | 119 (65·0) | 9 (82) | |
| Body, fundus, cardia | 64 (35·0) | 2 (18) | |
| Mean(s.d.) tumour size (cm) | 2·1(1·1) | 2·6(1·2) | 0·113† |
| Tumour depth | | | 0·295‡ |
| Mucosa | 19 (10·4) | 0 (0) | |
| SM1 | 30 (16·4) | 1 (9) | |
| SM invasion depth ≥ 500 μm | 134 (73·2) | 10 (91) | |
| Differentiation | | | 0·128 |
| Well differentiated | 37 (20·2) | 0 (0) | |
| Moderately differentiated | 146 (79·8) | 11 (100) | |
| Lymphovascular invasion | | | 1·000 |
| No | 76 (41·5) | 5 (45) | |
| Yes | 107 (58·5) | 6 (55) | |

Values in parentheses are percentages unless indicated otherwise. LN, lymph node; SM1, submucosal invasion depth less than 500 μm from muscularis mucosa layer; SM, submucosal. *$\chi^2$ test, except †Student's *t* test. ‡Mucosa or SM1 *versus* SM invasion depth of 500 μm or more.

neutral buffered formalin for more than 12 h for fixation. After fixation, the specimen was sectioned serially at 2-mm intervals parallel to a line that included the closest resection margin so that both lateral and vertical margins could be assessed. The depth of tumour invasion was then evaluated along with lymphovascular involvement and degree of differentiation[1]. According to Korean and Japanese guidelines, early gastric cancer, consisting of components of both differentiated-type carcinoma and poorly differentiated or signet ring cell carcinoma, was classified according to the predominant histological type[3,13].

## Follow-up after endoscopic resection

For patients undergoing rescue radical gastrectomy with D2 lymph node dissection after non-curative endoscopic resection of early gastric cancer, oesophagogastroduodenoscopy was performed 3 months after additional surgery. Thereafter, oesophagogastroduodenoscopy and abdominal CT were carried out annually and biannually respectively for 3 years, then annually from the fourth to fifth years.

For patients undergoing no additional treatment, oesophagogastroduodenoscopy was performed 2 months after endoscopic resection. Thereafter, oesophagogastroduodenoscopy and abdominal CT were carried out biannually for 3 years, and annually from the fourth to the fifth years.

## Statistical analysis

Categorical data were analysed using $\chi^2$ test or Fisher's exact test, and continuous data by means of Student's *t* test. Data on overall survival were obtained from the national registry of medical insurance. Overall survival was measured from the date of endoscopic resection to the date of death from any cause or to the censoring date of 31 May 2014. Overall survival rates were calculated using the Kaplan–Meier method and analysed by the log rank test. Multivariable analysis was undertaken using a Cox proportional hazards model to explore the potential association between overall survival and clinicopathological parameters (age, sex, Charlson co-morbidity index score[14], additional treatment, tumour depth, lymphovascular invasion and tumour size). $P < 0{\cdot}050$ was considered statistically significant.

# Results

Between April 2000 and May 2011, a total of 2036 consecutive patients with 2091 differentiated-type early gastric cancer lesions underwent their first EMR or ESD at Samsung Medical Centre. A total of 341 patients (16·7 per cent) underwent non-curative endoscopic resection of at least one lesion. After excluding 67 patients who had a positive lateral resection margin as the only non-curative factor, 274 patients with 281 differentiated-type early gastric cancer lesions were finally enrolled in the study (*Fig. 1*).

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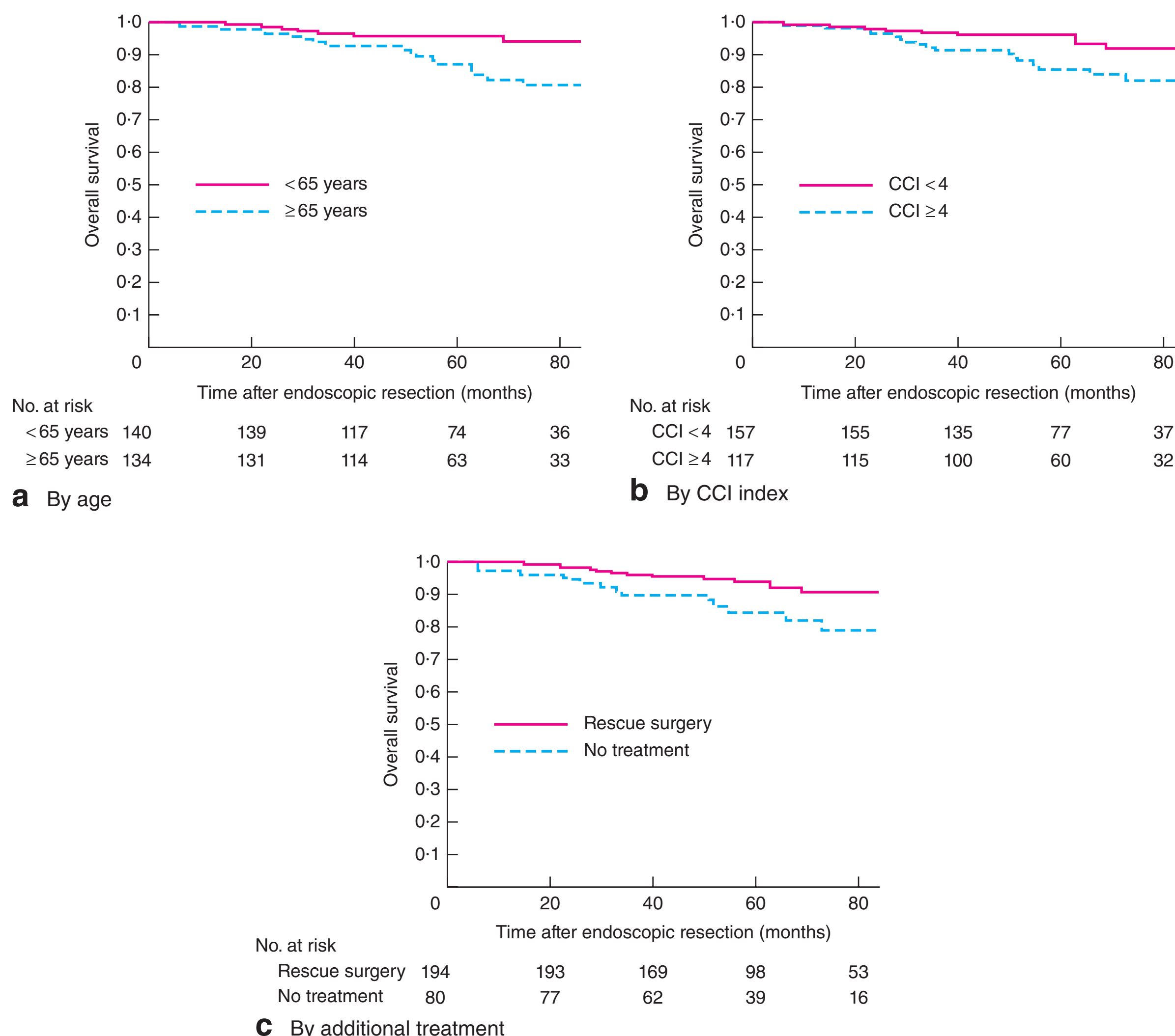


**Fig. 2** Kaplan–Meier overall survival curves for patients undergoing non-curative endoscopic resection of early gastric cancer according to: **a** age, **b** Charlson co-morbidity index (CCI) score and **c** type of treatment. **a** $P = 0{\cdot}009$, **b** $P = 0{\cdot}016$, **c** $P = 0{\cdot}028$ (log rank test)

Some 194 of the 274 patients underwent additional radical gastrectomy with D2 lymph node dissection within 6 months after endoscopic resection (rescue surgery group) and 80 patients were followed up without any additional treatment (no-treatment group). Two patients who had additional surgery 21 and 38 months after endoscopic resection were included in the no-treatment group. The reasons for not performing rescue surgery within 6 months after endoscopic resection were patient refusal of surgery (64), high surgical risk owing to severe co-morbidities (8) and concomitant advanced cancer in other organs (8).

*Table 1* compares the clinicopathological characteristics of patients who had rescue surgery and those who received no further treatment. Patients in the rescue surgery group were significantly younger, with a lower Charlson co-morbidity index score, smaller tumours and a higher lymphovascular invasion rate. All 21 patients with mucosal cancer had lymphovascular invasion and so were included in the study.

## Clinicopathological characteristics of patients undergoing rescue surgery according to the presence of lymph node metastasis

Among the 194 patients who had rescue surgery, intragastric local residual tumours were found in ten patients (5·2 per cent) and lymph node metastases in 11 (5·7 per cent). All patients with local residual tumours had tumour

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**Table 3** Results of multivariable Cox proportional hazards analysis to determine predictors of overall survival

| | *n* | 5-year overall survival (%) | Hazard ratio | *P* |
|---|---|---|---|---|
| Age (years) | | | | |
| < 65 | 140 | 95·6 | 1·00 (reference) | |
| ≥ 65 | 134 | 87·0 | 2·05 (0·72, 5·85) | 0·181 |
| Sex | | | | |
| M | 205 | 90·3 | 1·00 (reference) | |
| F | 69 | 95·0 | 0·43 (0·14, 1·27) | 0·127 |
| Charlson co-morbidity index score | | | | |
| < 4 | 157 | 96·1 | 1·00 (reference) | |
| ≥ 4 | 117 | 85·5 | 1·38 (0·53, 3·63) | 0·513 |
| Additional treatment | | | | |
| No treatment | 80 | 84·7 | 1·00 (reference) | |
| Rescue surgery | 194 | 94·3 | 0·43 (0·18, 1·00) | 0·049 |
| Tumour depth | | | | |
| Mucosa or SM1 | 76 | 92·8 | 1·00 (reference) | |
| SM invasion depth ≥ 500 μm | 198 | 90·9 | 1·56 (0·62, 3·96) | 0·345 |
| Lymphovascular invasion | | | | |
| No | 138 | 92·1 | 1·00 (reference) | |
| Yes | 136 | 90·7 | 1·72 (0·76, 3·87) | 0·191 |
| Tumour size (cm) | | | | |
| < 2 | 126 | 94·0 | 1·00 (reference) | |
| ≥ 2 | 148 | 89·0 | 1·02 (0·46, 2·27) | 0·965 |

Values in parentheses are 95 per cent c.i. SM1, submucosal invasion depth less than 500 μm from muscularis mucosa layer; SM, submucosal.

involvement of resection margins in the endoscopic resection specimen. No local residual tumours were found in any patient with lymph node metastases, and vice versa. *Table 2* shows the clinicopathological characteristics of 194 patients undergoing rescue surgery according to the presence of lymph node metastasis. Patients with lymph node metastasis were significantly older than those without. There was no significant difference in tumour size, depth, differentiation or lymphovascular invasion rate between the two groups. No patient with well differentiated histology or mucosal cancer showed lymph node metastasis. There was only one patient with SM1 cancer among patients with lymph node metastasis (*Fig. 1*; *Fig. S1*, supporting information). This man had a 4·4-cm cancer with a submucosal invasion depth of up to 250 μm. No lymphovascular invasion was found in the resection specimen. Pathological review of the resection specimen revealed histological heterogeneity, with a poorly differentiated carcinoma component accounting for 15 per cent of the total tumour area.

Among 11 patients with lymph node metastasis, the median number of harvested lymph nodes was 34 (range 21–60). Eight patients had metastasis to one lymph node and three patients had metastasis to two nodes. In nine patients, the lymph node metastasis was confined within the N1 station. In two of the 11 patients, however, lymph node metastasis was found beyond the N1 station[3]: in 8a in one and 12a in the other patient.

## Overall survival after endoscopic resection

The median duration of follow-up after endoscopic resection was 60·5 (range 6–141) months. Univariable analysis showed that patients aged less than 65 years, those with a Charlson co-morbidity index score below 4, and patients undergoing rescue surgery had significantly longer overall survival (*Fig. 2*). Tumour invasion depth, presence of lymphovascular invasion and tumour size did not influence overall survival. Five-year overall survival rates for patients who had rescue surgery and those who received no additional treatment were 94·3 and 85 per cent respectively. In the Cox proportional hazards model, rescue surgery was identified as the only independent predictor of overall survival in patients who underwent non-curative endoscopic resection of early gastric cancer (hazard ratio 0·43, 95 per cent c.i. 0·18 to 1·00; $P = 0·049$) (*Table 3*).

During follow-up, five patients (6 per cent) in the no-treatment group and one (0·5 per cent) in the rescue surgery group showed progression to advanced gastric cancer; five of these patients had distant metastasis (*Fig. 1*). All six patients with progression to advanced gastric cancer had both submucosal tumour invasion and lymphovascular involvement of tumour. None of the patients with SM1 cancer without lymphovascular invasion, or mucosal cancer with lymphovascular invasion showed progression to advanced gastric cancer during follow-up. The interval between endoscopic resection and progression to advanced gastric cancer ranged from 21 to 40 months.

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Gastric cancer-related deaths occurred in two patients (3 per cent) who received no further treatment and one (0·5 per cent) who had rescue surgery.

## Discussion

This study found a survival benefit for patients who underwent rescue surgery after non-curative endoscopic resection for early gastric cancer, regardless of age.

In the previous studies of patients undergoing rescue surgery following non-curative endoscopic resection of early gastric cancer, the lymph node metastasis rate ranged from 5·8 to 8·2 per cent[7,15,16], similar to the present finding of 5·7 per cent. These rates of lymph node metastasis were lower than those reported in the general early gastric cancer population[2]. The operative mortality rate associated with radical gastrectomy was less than 1 per cent in Korea and Japan[7,17,18]. Therefore, the lymph node metastasis rate of 5·7–8·2 per cent has clinical implications and can significantly affect prognosis. Risk factors for lymph node metastasis in early gastric cancer identified from a large surgical study[2] included large tumour size, submucosal deep tumour invasion, undifferentiated histology and lymphovascular invasion. In contrast to the results from the general early gastric cancer population, the present study showed no significant difference in tumour size, tumour depth, differentiation or lymphovascular invasion rate between patients with and without lymph node metastasis. Only age differed significantly between the two groups. These results were similar to those from a previous study[15] of 147 patients who had rescue surgery following non-curative endoscopic resection of early gastric cancer, which found no significant difference in tumour depth, differentiation or lymphovascular invasion rate between patients with and those without lymph node metastasis; only tumour size was significantly different between the two groups (2 cm or less *versus* more than 2 cm). The differences in findings for patients undergoing rescue surgery compared with those for the general early gastric cancer population were likely due to the selection of patients appropriate for endoscopic resection and the small number of patients with lymph node metastasis among those undergoing non-curative endoscopic resection for early gastric cancer, which might have limited the statistical power. Although not statistically significant, both the present study and that of Son and colleagues[15] showed that deep tumour invasion was more common among patients with than in those without lymph node metastasis (91 and 73·2 per cent respectively in the present study; 91·7 and 66·7 per cent reported by Son *et al.*). In the present study, no patient with well differentiated histology or mucosal cancer had lymph node metastasis. However, previous studies[15,16] reported the presence of lymph node metastasis in such patients[15,16].

The distribution of lymph node metastasis and required range of lymph node dissection are other issues in patients undergoing non-curative endoscopic resection of early gastric cancer. Metastasis beyond the N1 station was found in two of 11 patients with lymph node involvement in the present study and 25·0 per cent in the study by Son and colleagues[15]. Therefore, at least D1+ lymph node dissection should be considered primarily in these patients.

It remains controversial whether rescue surgery following non-curative endoscopic resection of early gastric cancer improves prognosis. Oda and co-workers[7] reported comparable 5-year survival rates of 97·8 and 91 per cent respectively in patients who did and did not undergo rescue surgery. Gastric cancer-related deaths occurred in 2·1 and 2·4 per cent respectively. That study included undifferentiated-type early gastric cancers with a high potential for lymph node metastasis as well as differentiated-type early gastric cancers, which might explain the similar 5-year survival rates. In another study[10], the 5-year survival rate was 95 per cent among patients who had rescue surgery and 63 per cent in those who did not. The latter patients had a significantly shorter survival than patients who had curative endoscopic resection for early gastric cancer. However, that study was limited because there was no direct comparison of survival rates between patients with and without rescue surgery following non-curative endoscopic resection, and only elderly patients (aged over 75 years) were included. The rate of gastric cancer-related death was zero in the rescue surgery group and 4·9 per cent in the no-treatment group. In the present study, patients who had rescue surgery had a significantly longer overall survival than those who received no additional treatment. In multivariable analysis adjusted for age and co-morbidity, rescue surgery was the only independent predictor of overall survival in patients who had non-curative endoscopic resection of early gastric cancer. Gastric cancer-related death rates were 0·5 and 3 per cent in the rescue surgery and no-treatment groups respectively. These figures might be underestimated as not all patients completed the 5-year follow-up after endoscopic resection or rescue surgery.

This study is limited in that it was performed at a single tertiary referral centre and had a retrospective design. In addition, the treatment strategy after non-curative endoscopic resection of early gastric cancer was not randomized between rescue surgery and close observation. Individual factors such as age, co-morbidity and patient preference could have affected treatment decisions. However, the

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study had several strengths. First, the study population was large, and the subjects were enrolled consecutively from a prospectively collected database. Second, follow-up after endoscopic resection or rescue surgery was performed according to a standard protocol. Finally, multivariable analysis adjusted for age and co-morbidity was used to identify independent predictors of survival. This approach might minimize the probable bias from individual factors.

## Acknowledgements

E.R.K. and H.L. contributed equally to this work.
*Disclosure:* The authors declare no conflict of interest.

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## Supporting information

Additional supporting information may be found in the online version of this article:

**Fig. S1** Endoscopic and histopathological views of early gastric cancer (Word document)

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