

Prevalence and risk factors for malignant nodal involvement in early esophago-gastric adenocarcinoma: Results from the multicenter retrospective CONGRESS study (endoscopic resection, esophagectomy or gastrectomy for Early esophago-gastric cancerS)

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In addition, the above named collaborators have contributed time and energy to contribute to their data, without them this project could not have been completed.

Abstract

Objective

The aim of this study was to quantify LNM risk and outcomes following treatment of early esophago-gastric (EG) adenocarcinoma.

Background

The standard of care for early T1N0 EG cancer is endoscopic resection (ER). Radical surgical resection is recommended for patients perceived to be at risk of lymph node metastasis (LNM). Current models to select organ-preserving vs. surgical treatment are inconsistent.

Methods

CONGRESS is a UK-based multicentre retrospective cohort study. Patients diagnosed with clinical or pathological T1N0 EG adenocarcinoma from 2015-2022 were included. Outcomes and rates of LNM were assessed. Cox regression was performed to assess the impact of prognostic and treatment factors on overall survival.

Results

1,601 patients from 26 centres were included, with median follow-up 32 months (IQR 14-53). 1285/1612 (80.3%) underwent ER, 497/1601 (31.0%) underwent surgery. Overall rate of LNM was 13.5%. On ER staging, tumour depth (T1b sm2-3 17.6% vs. T1a 7.1%), lymphovascular invasion (17.2% vs. 12.6%), or signet cells (28.6% vs. 13.0%) were associated with LNM. In multivariable regression analysis, these were not significantly associated with LNM rates or survival. Adjusting for demographic and tumour variables, surgery after ER was associated with significant survival benefit, HR 0.33 (0.15-0.77), $p=0.010$.

Conclusion

This large multicentre dataset suggests that early EG adenocarcinoma is associated with significant risk of LNM. This data is representative of current real clinical practice with ER-based staging, and suggests previously held beliefs regarding reliability of predictive factors for LNM may need to be reconsidered. Further research to identify patients who may benefit from organ-preserving vs. surgical treatment is urgently required.

Introduction

Whereas surgical resection was once the mainstay of treatment for management of early (T1N0) esophago-gastric (EG) adenocarcinoma, endoscopic resection (ER) is now the accepted standard and in many cases is thought to offer curative organ-preserving treatment. Radical surgery is associated with major morbidity risk¹ and deleterious effect on quality of life^{2,3}. It is generally reserved for tumours with high-risk features which are believed to place patients at high risk of lymph node metastasis (LNM), which cannot be addressed through ER.⁴⁻⁶ Such features are generally considered to include the presence of lymphovascular invasion (LVI) or submucosal invasion to a depth of greater than 500 µm (T1b sm2+); some guidelines additionally include poorly differentiated tumours.^{4,5}

Counselling patients on their potential LNM risk, and whether to pursue surgical resection, is challenging. There is some disagreement between international guidelines on what risk factors must be considered.⁴⁻⁶ Furthermore, estimation of the theoretical risk of LNM conferred by these risk factors is based almost exclusively on historical analyses of small case series of predominantly surgical specimens, consisting typically of 50-200 patients.⁷⁻¹⁰ Estimating LNM risk for ER specimens, using published data from surgical specimens, is problematic due to differences in the way that ER and surgical specimens are prepared and variability in pathological assessment, with potential understaging in surgical specimens.^{10,11} Available data is thus highly heterogeneous, with reported LNM rates for T1N0 disease ranging from <2% for T1a disease¹⁰ to as high as 50% or more in higher risk tumours.^{12,13}

A large scale granular dataset is urgently needed to better understand risks, management, and outcomes of early EG cancer, and guide patient counselling and joint decision-making. The aim of this study was to quantify LNM risk and outcomes following treatment of early EG adenocarcinoma with curative intent in a large multi-centre dataset.

Methods

Study design and setting

CONGRESS (endoscopic resection, esophagectomy or gastrectomy for Early esophagogastric cancer) was conducted as a multicentre retrospective cohort study with a

structure modelled on, and methodology developed in partnership with members of, previous international research collaboratives.^{1,14,15} A database capturing diagnostic, demographic, treatment and outcome variables was designed and piloted by a multidisciplinary steering group which included surgeons, oncologists, gastroenterologists, and methodologists. This database was transcribed to an online platform for anonymised data submission (Research Electronic Data Capture, REDCap).

Open invitations to participate were circulated via specialist societies, social media, and personal communication with a predominant focus on UK centres; EG cancer management in England and Wales is centralised to 35 tertiary hospitals. In addition to UK centres, 1 Swedish centre (Karolinska Institutet) also took part. Each centre's local lead was responsible for ensuring their own relevant ethical permissions and study registration to comply with local protocols.

Inclusion criteria

Patients diagnosed 2015-2022 (inclusive) were eligible for inclusion, with the follow-up period extending until the database closure date in July 2023.

The aim was to capture outcomes for all patients who received treatment with curative intent for T1N0 cancer, based on available staging. In order to capture real-world outcomes for T1N0 disease, the allowed diagnostic criteria were pragmatic and included any patients with cT1N0 undergoing curative therapy, as well as patients undergoing surgery or ER for high-grade dysplasia (HGD) with subsequent pT1N0 – as these would also be subject to the same decision-making regarding subsequent surveillance or surgery. Only patients with a histological diagnosis of adenocarcinoma, or initially columnar dysplasia, were included in this analysis. Patients who received palliative or no treatment for any reason were excluded.

Data capture

Demographic data included age, gender, and comorbidities. Initial diagnostic data and up to three treatment rounds were captured to account for patients who may have had initial ER followed by additional treatment (including repeat ER, surgery, or oncological therapy). Clinical and survival outcomes were recorded.

Statistical analysis

Patient who underwent surgery were compared with those that did not using appropriate non-parametric statistical tests (Chi square and Kruskal-Wallis). Predictive factors for LNM were compared with final surgical specimen pathology.

To assess differences between LNM risk for ER and surgical specimen-based staging within the same patient group, we compared histopathological findings, along with corresponding LNM risk, for the patients who underwent ER followed by surgery. Where the surgical specimen contained no residual primary tumour, endoscopic pathological results were used.

Multi-variable regression was performed to assess the feasibility of a predictive model for LNM risk following ER based on demographic, clinical and pathological variables. Factors affecting overall survival were assessed using multi-variable Cox regression analysis.

Missing data was handled by multiple imputation by chained equations. $p < 0.05$ was considered statistically significant. STROBE guidelines were adhered to in reporting of results (see supplemental data appendix 1, Supplemental Digital Content 1, <http://links.lww.com/SLA/F289>).

Results

A total of 1,841 patients from 26 centres were included. Median follow up was 32 months (IQR 14-53). Further analysis was confined to patients with confirmed adenocarcinoma or columnar type high grade dysplasia (HGD), giving a cohort size of 1,601 (1197

Adenocarcinoma, 404 HGD). Data collection was good, with low rates of data missingness: <1% in initial staging and surgical outcome data. Missingness of endoscopic resection pathology data was <1% for tumour depth, differentiation, and presence of signet cells, 11% for LVI.

Initial clinical staging (see table 1) for these patients was T1 in 978 (61.1%), TX for 348 (21.8%) and T0 or HGD in 274 (17.1%). Initial staging investigations performed were variable and more common in patients with confirmed adenocarcinoma, and included CT scan (73%), PET (30.5%), endoscopic ultrasound (31.5%), and staging laparoscopy (6.5%). Initial management of these patients was predominantly endoscopic resection (1285/1601, 80.3%), of which 217/1285 (16.9%) of patients went on to have surgery based on high-risk features or patient preference (see figure 1). 271/1601 (16.9%) of patients were primarily

managed with surgery. Where a reason was given, most patients who went straight to surgery were either deemed not endoscopically resectable (170/270 valid responses, 62.9%), or in a small number of cases underwent primary surgery due to patient choice (22/270, 8.1%). Ultimately 497 patients (31.0% of all patients) with clinically early disease at presentation underwent radical surgery.

Patient demographics

Median patient age was 71 years. Patients were predominantly male, with distal esophageal tumours (see table 2). When comparing patients undergoing surgery versus those who did not, surgical patients were more likely to be younger (68 v 72y, $p<0.001$), have a Charlson comorbidity score of 0 (59.2% vs 46.5%, $p<0.001$), and had more advanced tumours, with a greater proportion of surgical patients demonstrating poorly differentiated tumour cells (23.3% vs. 8.5%, $p<0.001$), present signet cells (8.9% vs. 2.1%, $p<0.001$), or less favourable cT stage (T1b 22.3% vs. 9.1%, $p<0.001$).

Procedural outcomes

Following endoscopic resection, no complications were reported in 1198/1285 (93.2%) of cases. The most common reported complications included bleeding in 42/1285 (3.3%) and perforation in 11/1285 (0.9%) of cases.

Considering patient outcomes after radical surgery, where outcome data was available, complications occurred in 284/453 patients (62.7%), which were of Clavien-Dindo grade 1 or 2 in 168 patients (37.0%), grade 3a in 41 (9.1%), 3b in 28 (6.1%), 4 in 38 (8.4%). In-hospital mortality was 2.0% (9 patients). The median length of stay was 10 days (IQR 7-17.75), and a median of 22 lymph nodes were harvested in each case (IQR 15-31).

Predictors of lymph node metastasis

The overall rate of surgical specimen LNM was 67/497 (13.5%). As expected, more advanced nodal stage corresponded to worse survival ($p=0.006$, see supplemental data appendix 2, Supplemental Digital Content 1, <http://links.lww.com/SLA/F289>). Assessing histopathology of all surgical specimens, where recorded, LVI was present in 85/473 cases

(17.9%). Tumour cell differentiation was poor in 107/459 (31.8%). Signet ring cells were present in 47/494 (9.5%).

When comparing ER-based and subsequent surgical pathological staging variables for the subset of patients who underwent surgery after ER, there was significant discordance between endoscopic and surgical staging. Of the patients who underwent ER followed by surgery, 110 patients had R0 resection with complete pathological data, of which 40 (36%) had subsequent surgical specimen pathology exhibiting discordant T stage or LVI status (see figure 2). The overall rate of LNM for this group was 13.8% (30/217). The rate of LNM across varying T stages was T1a = 9.8%, T1b sm1 = 14.8%, T1b sm2-3 = 17.9%. Significant rates of LNM were seen in patients without any reported ER pathological risk factors (i.e. patients without any of the following risk factors: positive deep or circumferential ER margins, poor differentiation, or T1b sm2 or greater depth of invasion), 8/52 (15.3%). Comparing rates of N+ between ER and surgical specimens (table 3), analyses of surgical specimens returned less advanced tumours (lesser T stage, lower incidence of poorly differentiated tumours or LVI) ($p < 0.001$ for all comparisons), but higher rates of LNM, suggesting overall potential understaging in surgical specimens.

Cross tabulated by ER-derived LVI, differentiation, and T stage, the number of patients for each subgroup were low; surgical specimens positive for LNM were however seen across almost all groups (see figure 3).

Multi-variable regression analysis to derive a prognostic model for LNM based on histological and demographic variables resulted in a statistically non-significant model with poor calibration (see supplemental data appendix 3, Supplemental Digital Content 1, <http://links.lww.com/SLA/F289>).

Cox regression analysis for overall survival

For all patients, after adjusting for age, sex, Charlson comorbidity score, tumour site, histological subtype, differentiation, Barrett's, presence of signet cells and cT stage prior to treatment see supplemental data appendix 4, Supplemental Digital Content 1, <http://links.lww.com/SLA/F289>), age (HR 1.07, 95% CI 1.05-1.09, $p < 0.001$) and Charlson score 0 (0.57 (0.44-0.74), $p < 0.001$) were significantly associated with survival. In terms treatment variables, surgery was not significantly associated with survival advantage for unselected patients (HR 0.72, 95% CI 0.50-1.03, $p = 0.070$).

Analysing only patients who underwent ER, after adjusting for demographic and disease variables (see table 4), a significant survival benefit was seen for patients undergoing surgery (HR 0.33 (0.15-0.77), $p=0.010$), with poorer survival for older patients (1.08 (1.05-1.011), $p<0.001$), $p=0.001$) and positive ER circumferential margin (2.51 (1.47-4.29), $p=0.001$).

Discussion

CONGRESS represents the largest known granular dataset (containing detailed demographic, disease, and outcome data) for early EG cancer to date, presenting contemporary management strategies and real-world outcomes for 26 centres. The overall rate of LNM of 13.5% is higher than has been reported in previous series, with one pooled analysis suggesting rates of 4% for T1a and 23% for T1b disease.¹⁶ Previously reported histological risk factors such as LVI, T stage, and cell differentiation grade did not exhibit clear association when comparing ER staging to LNM risk or overall survival. In multi-variable Cox regression analysis, surgery was associated with a strong survival benefit after primary ER.

In modern clinical practice, the need to decide between either organ-preserving or surgical therapy is predominantly informed by ER-based pathological staging. Predictive models for LNM should therefore be based upon ER specimen pathology, rather than surgical pathology, if they are to be valid. Published prediction models for LNM in T1b cancer exemplify the limitations of existing reports in that such studies are often based on surgical specimens (rather than ER), low numbers, and outdated practice: Lee et al¹⁷ reported a risk prediction system for LNM in T1 disease based upon 258 surgical specimens from 5 institutions over 11 years (2000-2011), whereas Gotink et al¹⁸ included 248 patients treated predominantly with primary surgery between 1989-2016. These data should therefore not be used to predict LNM based on ER. ER specimens are assessed differently (with typically smaller slices prepared for analysis and therefore closer scrutiny); surgical specimens after ER may also contain multifocal or residual disease with different final staging. The known variability in the assessment of surgical specimens¹⁹ is thought to further contribute to potential understaging of disease if considering surgical specimens alone.

In the present dataset, despite large patient numbers, we did not find a significant association between pathological variables and LNM risk. This is a substantial finding which calls into question the validity of preoperative counselling of patients based on initial histopathological

data. It also calls into question the validity of previous risk assessment studies, many of which were based upon surgical pathology rather than ER. It may be that the increasingly recognised heterogeneous nature of EG cancer, and interaction of multiple risk factors, means that it is difficult or impossible to accurately predict this from endoscopic specimens. It is equally possible, however, that discordance in this this real world multicentre dataset instead reflects the known variability in staging workup discordant reporting between pathologists.^{19–22} The variability of staging investigations also suggests that improvements in the standardisation of workup of these patients may be required which could improve the pre-treatment detection of nodal metastases, though some reports have highlighted that CT and PET-CT may be of limited sensitivity or utility in HGD or early cancer.²³ Differences in specimen preparation and pathologist variation may mean that relevant risk factors may be more or less likely to be identified on pathological assessment. Current UK guidelines recommend joint assessment of specimens by two pathologists, one of who should be a gastrointestinal specialist, for Barrett's dysplasia only;²⁴ data on the number and specialist interest of pathologists involved in the CONGRESS specimens was not collected. The number of T1a tumours which went forward to surgery also reflects the importance of other non-pathological considerations which might influence the need for surgery, such as endoscopic appearances or multi-focal disease, which were not recorded in this dataset. Other factors such as variable time intervals (and potentially resulting tumour progression) between ER and surgery may further complicate pathology-based risk assessment. These issues highlight the need for detailed and prospective study to better understand factors associated with LNM risk. Without a standardised, reliable assessment of specimens, it may not be possible to adequately assess individual patient prognosis based on ER alone.

This inability to identify a significant pattern of multi-factorial adjusted risk factors, both for LNM in regression analysis as well as overall survival in Cox regression, in the CONGRESS dataset, further complicates the existing dilemma of how to counsel patients with clinically staged early EG cancer. First, over 10% of all patients with tumours that were endoscopically staged T1b sm1 or less, traditionally thought to be the lowest risk group, were found to have LNM at surgery, without any significant association to LVI or tumour differentiation status. Should all patients with early EG cancer, regardless of stage, be offered surgical consultation? Second, what is an acceptable risk for LNM? The American Gastroenterological Association alludes to a “minimal chance” of LN or distant metastasis as representing <2% and that a perceived risk above this should be considered for surgery.⁵

Justification of such a threshold is sometimes given as surgery being considered a viable option if the risk of LNM outweighs the risk of mortality after esophagectomy. However, this discounts the significant consequences of undergoing surgery, such as at least temporarily decreased quality of life, and does not consider the fact that patients may accept differing degrees of risk. Some patients may desire maximal risk reduction, or to avoid the recurrent interventions and potential anxiety associated with surveillance, and be more likely to request surgery. In contrast, other patients may wish instead to maximise their quality of life with organ-preserving treatment (ER), and may accept a potentially discounted life expectancy in return for avoiding surgery even in higher-risk tumours.^{25,26} There remains also a question about the potential efficacy of adjuvant therapies such as chemotherapy, radiotherapy, or brachytherapy, which could potentially further contribute to disease control after ER in early EG cancer.

The findings of this study, that surgery is significantly associated with improved overall survival in early EG cancer after ER, is at odds with some other published findings. Tankel et al²⁷ reported equivalent survival for surveillance and esophagectomy after ER of high risk T1b esophageal cancer, however this was in a small patient group, with only 27 patients in the observation group over a study period of 11 years (2012-2022). Kamarajah et al²⁸ reported a large US (National Cancer Data Base, NCDB) analysis of patients with T1a and T1b esophageal cancer; ER had equivalent long-term survival compared to primary surgery after propensity score matching for demographic and disease variables. However, the database does not account for differences in ER and surgical staging. Surgical specimens were therefore potentially understaged compared to ER, and represented in fact more advanced disease (and thus benefitted from esophagectomy). An analysis by the same group of gastric cancer data found that ER was inferior to surgery for gastric cancers.²⁹

Data for CONGRESS were entered through a collaborative group model based on previously successful studies with many of the same personnel^{1,15}; levels of data missingness were low and surgical outcome data entered into the CONGRESS database closely mirror those reported in the compulsory UK national EG cancer database (NOGCA),³⁰ strongly supporting the internal validity of this dataset. In multi-variable Cox regression analysis, CONGRESS data have suggested that surgery after ER is associated with improved overall survival – however, significant differences between groups and an absence of cause of death or recurrence data mean that some of this difference may result from incomplete adjustment within the regression model, highlighting the need for prospective study. Furthermore, the

lack of data on disease-related mortality or recurrence type (local, nodal, or systemic), limits some of the conclusions that can be drawn. The relatively high incidence of LNM even in ER-staged low risk groups is surprising, and suggests the possible presence of additional risk factors not captured here or addressed in current guidelines. Despite the large numbers of included patients, cross tabulated analysis of histological subgroups also resulted in small numbers for each group when assessing for LNM risk which suggests a sample size limitation for statistical analysis. The real-world and contemporaneous nature of this data, however, strongly supports the generalisability of the reported findings to daily clinical decision-making in current practice. Novel treatments such as sentinel lymph node biopsy³¹ may in future offer an alternative to radical surgery, but are not yet proven.

Patients with early EG cancer, along with their clinicians, face a dilemma when it comes to deciding on the optimal treatment modality. Based upon this large predominantly UK-based dataset, the risk of LNM appears greater, and less predictable in current practice, than previously reported. Many of these findings are discordant with currently accepted evidence, suggesting an urgent need for re-evaluation of staging, treatment, and quality control processes. This data should be used to inform joint decision making, and highlights the need for urgent prospective study.

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Figure 1. Flowchart of patients meeting inclusion criteria and treatment pathway. (ER:endoscopic resection)

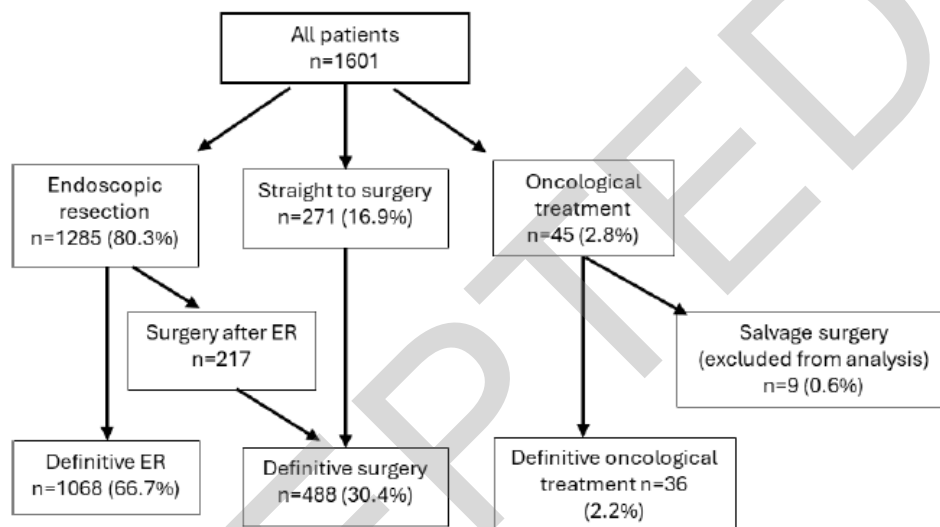
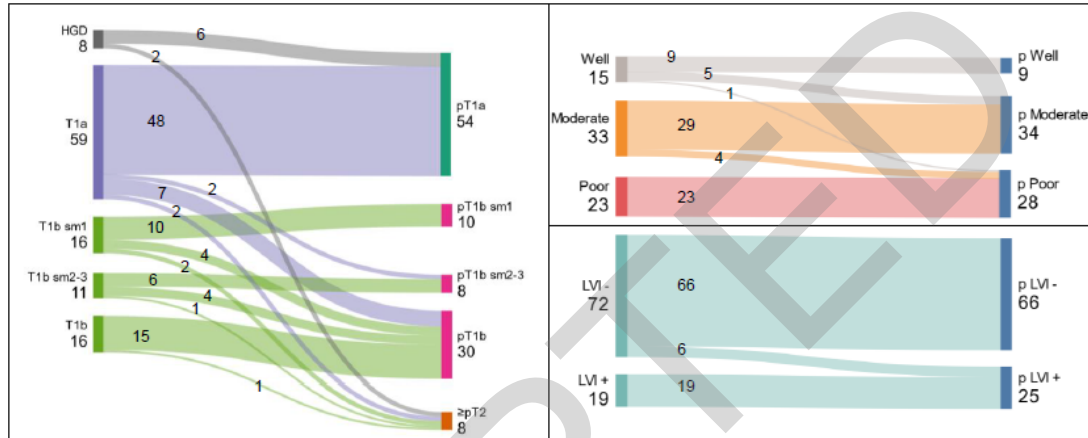


Figure 2. Flowchart illustrating differences between ER and final (surgical) pathology for patients undergoing initial ER followed by surgery. Individual plots for T stage, worst tumour differentiation grade, and lymphovascular invasion (LVI). Patients with initial R1 ER margins excluded from this analysis.



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Figure 3. Observed nodal metastasis risk in patients undergoing surgery after endoscopic resection. Rates of nodal metastasis in surgical specimen, stratified by T stage, differentiation, and lymphovascular invasion seen on endoscopic resection specimen. Percentages with absolute numbers in parentheses. Numbers do not equate to total surgical volume as patients not included here if any missing histological data or initial pathology showed dysplasia only.

	LVI-	LVI+	
Well	11% (1/8)	0% (0/4)	≤T1a
Mod	13% (3/24)	0% (0/5)	
Poor	8% (1/12)	13% (1/8)	

	LVI-	LVI+	
Well	0% (0/2)	0% (0/3)	T1b sm1
Mod	13% (1/8)	25% (1/4)	
Poor	14% (1/7)	33% (1/3)	

	LVI-	LVI+	
Well	0% (0/1)	50% (2/4)	T1b (sm not reported)
Mod	7% (1/15)	40% (2/5)	
Poor	9% (1/11)	25% (2/8)	

	LVI-	LVI+	
Well	100% (2/2)	25% (1/4)	T1b sm 2/3
Mod	8% (1/12)	0% (0/4)	
Poor	20% (1/5)	0% (0/1)	

Table 1. Initial cT stage prior to index treatment

T stage	n	%
T0 (i.e. high-grade dysplasia)	274	17.1%
T1 (i.e. T1a/T1b not reported)	390	24.4%
T1a	375	23.4%
T1b	213	13.4%
Tx (i.e. cancer not visible on imaging, early cancer without explicit T stage)	348	21.8%

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Table 2. Patient demographics

	Overall	No Surgery	Surgery	p
n	1612	1115	497	
Age at diagnosis	71.00 [64.00, 77.00]	72.00 [65.00, 78.00]	68.00 [60.00, 74.00]	<0.001
Patient sex				0.798
Male	1272 (78.9)	879 (78.8)	393 (79.1)	
Female	339 (21.0)	235 (21.1)	104 (20.9)	
Missing	1 (0.1)	1 (0.1)	0 (0.0)	
Charlson score 0	812 (50.4)	518 (46.5)	294 (59.2)	<0.001
Site of Pathology				<0.001
Proximal Esophagus	9 (0.6)	5 (0.4)	4 (0.8)	
Middle Esophagus	104 (6.5)	76 (6.8)	28 (5.6)	
Distal Esophagus	870 (54.0)	639 (57.3)	231 (46.5)	
Gastro-esophageal Junction	383 (23.8)	290 (26.0)	93 (18.7)	
Stomach - cardia/body	126 (7.8)	62 (5.6)	64 (12.9)	
Stomach - distal/antrum/pylorus	120 (7.4)	43 (3.9)	77 (15.5)	
Pathology within Barrett's	1136 (70.5)	851 (76.3)	285 (57.3)	<0.001
Histology on Biopsy				<0.001
High grade dysplasia	404 (25.1)	331 (29.7)	73 (14.7)	
Adenocarcinoma	1208 (74.9)	784 (70.3)	424 (85.3)	
Extent of tumour differentiation				<0.001
Well	319 (19.8)	252 (22.6)	67 (13.5)	
Moderate	536 (33.3)	362 (32.5)	174 (35.0)	
Poor	211 (13.1)	95 (8.5)	116 (23.3)	
HGD	474 (29.4)	379 (34.0)	95 (19.1)	
Missing	72 (4.5)	27 (2.4)	45 (9.1)	
Presence of Signet Cells				<0.001
No	1538 (95.4)	1086 (97.4)	452 (90.9)	
Yes	67 (4.2)	23 (2.1)	44 (8.9)	
Missing	7 (0.4)	6 (0.5)	1 (0.2)	
Initial tumour T stage				<0.001
T0 / HGD	274 (17.0)	235 (21.1)	39 (7.8)	
T1 (subgroup not reported)	390 (24.2)	210 (18.8)	180 (36.2)	
T1a	375 (23.3)	308 (27.6)	67 (13.5)	
T1b	213 (13.2)	102 (9.1)	111 (22.3)	
Tx	348 (21.6)	251 (22.5)	97 (19.5)	
Missing	12 (0.7)	9 (0.8)	3 (0.6)	

Table 3. Comparison of surgical and ER pathology with subsequent LNM status for patients undergoing surgery after ER. Where no residual cancer was seen in the surgical specimen, final primary tumour staging was based on ER specimen.

	Surgical staging			ER staging		
	N0	N+	%N+	N0	N+	%N+
T stage						
T0	0	0	N/A	7	1	12.5%
T1a	73	4	5.2%	79	6	7.1%
T1b (not otherwise reported)	64	13	16.9%	45	10	18.2%
T1b sm1 (<=500um)	17	1	5.6%	25	5	16.7%
T1b sm2-3 (>500um)	22	2	8.3%	28	6	17.6%
T2 or greater	9	10	52.6%	1	0	0.0%
Worst differentiation grade						
Well	32	3	8.6%	28	6	17.6%
Moderate	77	10	11.5%	75	10	11.8%
Poor	55	14	20.3%	53	9	14.5%
Presence of LVI						
Yes	52	16	23.5%	48	10	17.2%
No	121	13	9.7%	111	16	12.6%
Presence of signet cells						
Yes	8	3	27.3%	5	2	28.6%
No	178	27	13.2%	180	27	13.0%

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Table 4. Multivariable Cox regression for overall survival in patients undergoing endoscopic resection as primary treatment (n=1118)

Variable	HR (95% CI)	P
Age	1.08 (1.05 - 1.11)	<0.001
Sex		
Male	ref	
Female	0.91 (0.52 - 1.58)	0.726
Charlson score = 0	0.75 (0.46 - 1.23)	0.253
Barrett's Esophagus	1.61 (0.85 - 3.06)	0.142
Site		
Proximal Esophagus	ref	
Middle Esophagus	2.86 (0.32 - 25.79)	0.350
Distal Esophagus	2.49 (0.32 - 19.09)	0.380
GOJ	2.3 (0.27 - 19.23)	0.443
Stomach (cardia/body)	2.3 (0.2 - 25.91)	0.501
Stomach (distal/antrum)	7.14 (0.69 - 73.73)	0.099
Worst Endoscopic pT		
Dysplasia	ref	
pT1a	4961669.71 (0 - Inf)	0.996
pT1bSM1	7956213.13 (0 - Inf)	0.996
pT1bSM2-3	3472217.36 (0 - Inf)	0.996
Worst Endoscopic Differentiation		
Good	ref	
Moderate	1.27 (0.69 - 2.36)	0.442
Poor	1.23 (0.56 - 2.66)	0.608
Signet Ring +	1.43 (0.65 - 3.15)	0.375
LVI +	0.63 (0.13 - 3.05)	0.566
Deep margin +	1.99 (1.08 - 3.67)	0.027
Circumferential Margin +	2.51 (1.47 - 4.29)	0.001
Surgery after ER	0.33 (0.15 - 0.77)	0.010