

Accuracy of the revised Vienna Classification for predicting postendoscopic resection outcomes for gastric and oesophageal neoplasms: a retrospective cohort study of patients from a UK tertiary referral centre

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ABSTRACT

Aims To review the effectiveness of the revised Vienna classification (rVC) at predicting histological outcome and defining the postendoscopic resection (ER) clinical management plan of gastro-oesophageal dysplasia and early neoplasia in a UK tertiary-centre population.

Methods This was a retrospective cohort study between November 2011 and May 2018. 157 patients from Salford Royal NHS Foundation Trust in the UK were included. The primary outcome was the histological results of postsurgical resection (SR) specimens compared with their post-ER rVC. The secondary outcome was overall survival rates of patients with category 4.4 and 5 of the rVC.

Results One-hundred and thirteen patients were diagnosed with category ≥ 4 of the rVC. 23 patients (20.4%) were referred for additional surgery, whereas 69 patients (61.1%) were on endoscopic surveillance only. 60.9% of post-SR specimens (14/23) revealed no residual neoplasia. 78.6% of these cancer-free specimens were classed as category 5 rVC. The overall 7-year survival rate of 25 patients with category ≥ 4.4 was 68% with causes of mortality not linked to upper gastrointestinal neoplasia. The overall 7-year and 3-year survival rates of category 4.4 and 5 were 73.6% and 50%, respectively, although age and comorbid state played a role.

Conclusions This study provides evidence of outcomes comparable to other reported cohorts for cases after ER in a single-centre UK population even at rVC 4.4/5. It suggests surgery may not be necessary in all cases due to the lack of residual disease and further refinement of the rVC category 5 may help guide management.

INTRODUCTION

Oesophagectomy and gastrectomy are still performed for non-invasive neoplastic lesions of the upper gastrointestinal (GI) tract.^{1–4} A minimally invasive alternative is endoscopic resection (ER), which is proven to have a higher safety profile and similar curative outcomes compared with surgery.^{1 2 5–7} ER is subdivided into endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) and is increasingly used to stage and treat lesions particularly in older patients. ESD allows for en bloc resection, whereas EMR is typically piecemeal. Both techniques allow

for judgement of vertical invasion, only piecemeal resection can lose orientation of the peripheral margin.

ER is not a perfect method for early gastro-oesophageal neoplasia management, especially when the resected lesions are invading the submucosal layer or fail to achieve curative criteria defined by the Japanese Classification of Esophageal Cancer (JES) and Japanese Classification of Gastric Cancer (JGCA).^{8–10} Patients are often referred for surgery after ER.¹¹ The decision to proceed to surgery depends on the likelihood of residual disease which can be assessed using the revised Vienna Classification (rVC).

Prior to the Vienna Classification, there were marked discrepancies between Western and Japanese histological categorisation of early lesions. To address this, groups of pathologists from 12 countries conducted slide seminars in Tokyo, Munich, Padua and Vienna from 1996 to 1998.¹ These meetings highlighted that conventional use of descriptive terminologies without uniform systems of classification into clinically relevant categories had contributed to wide interobserver disagreements.^{1 12 13}

Invasion was a crucial indicator of metastatic potential for a Western pathologist to reach a diagnosis of carcinoma. A lesion is invasive from a Western viewpoint when lamina propria is involved, whereas Japanese pathologists concentrate more on cytological changes (enlarged nuclei with variable size, loss of polarity and prominent nucleoli) and architectural changes (complex branching and budding of glands). As a result, Japanese pathologists frequently use the term ‘mucosal carcinoma’ without further clarifying the presence or absence of invasion into the lamina propria.¹² Studies revealed that 49% of histological slides were diagnosed as invasive carcinoma based on Japanese viewpoints, whereas only 23% with Western viewpoints.¹ Hence, intramucosal carcinoma was further amended as category 4.4 in the revised version (table 1, figure 1)^{1 13} and the significance of this being the risk of lymphovascular spread being increased as the neoplasia extends into the mucosa, whereas rVC category 5 extends into the submucosa (figure 2). With the use of the rVC, biopsy results suggestive of category >4 would at least be



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Table 1 The revised Vienna Classification of gastrointestinal epithelial neoplasia or dysplasia¹

Category	Diagnosis	Clinical management
1	Negative for neoplasia/dysplasia <i>Including normal, reactive, regenerative, hyperplastic, atrophic and metaplastic epithelium</i>	Optional follow-up.
2	Indefinite for neoplasia/dysplasia	Follow-up is needed because of uncertainty about the real nature of lesion.
3	Mucosal low-grade neoplasia (LGIN, low-grade adenoma/dysplasia)	Neoplasia is present but the risk of developing invasive carcinoma is low. Endoscopic resection or follow-up*.
4	Mucosal high-grade neoplasia 4.1—HGIN, high-grade adenoma/dysplasia 4.2—HGIN, non-invasive carcinoma (carcinoma in situ) 4.3—Suspicious for invasive carcinoma 4.4—Intramucosal carcinoma	Risk of invasion and development of metastases is increased. Local treatment, eg, endoscopic resection or local surgical resection would be indicated*.
5	Submucosal or deeper invasion by carcinoma	Risk of subsequent deeper invasion and metastases is so high that surgical resection is urgently needed; only withheld in cases with clinical contraindications.

HGIN, including both categories 4.1 and 4.2; intramucosal, invading into the lamina propria or muscularis mucosae.

*Choice of treatment will depend on the size of the lesion, the depth of invasion as assessed endoscopically, radiologically or ultrasonographically, the histological differentiation grade and on general factors such as the patient's age and comorbid conditions.

HGIN, high-grade intraepithelial neoplasia; LGIN, low-grade intraepithelial neoplasia.

considered for a local resection. Once a lesion is resected, the rVC can be used to differentiate between categories 4 and 5 for consideration of additional treatment options.¹

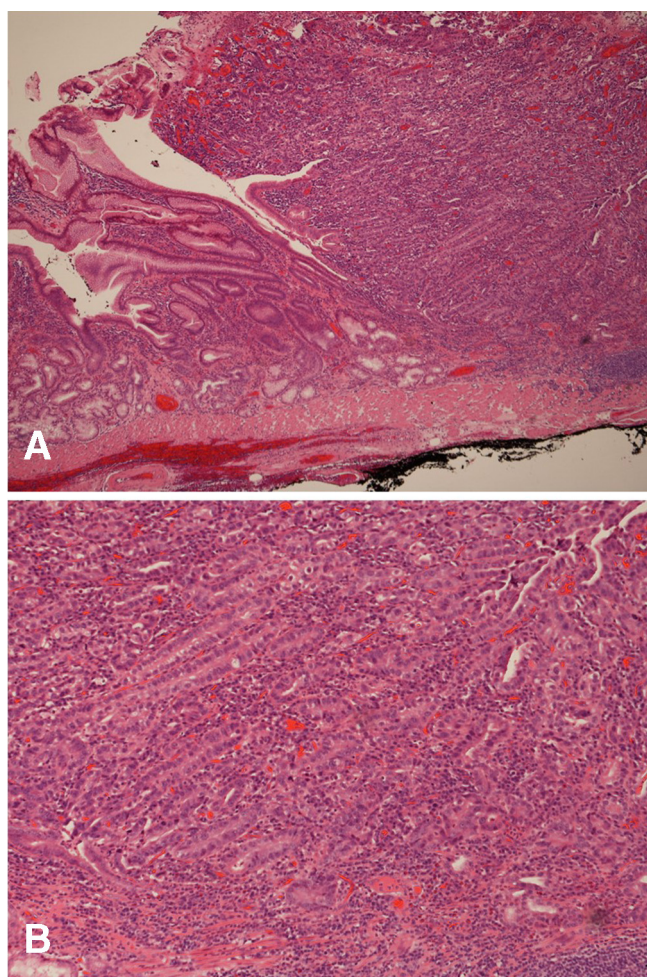


Figure 1 (A) H&E stained section demonstrating intramucosal adenocarcinoma of intestinal type at $\times 4$ magnification. The tumour is present on the right hand side of the section and the muscularis mucosa is clearly demonstrated at the deep aspect. (B) H&E stained section of the same specimen viewed at $\times 10$ magnification.

The accuracy and precision of the rVC has predominantly focused on establishing uniformed consensus between Western and Japanese histological viewpoints.^{1 12 13} To our knowledge, no studies have investigated the effectiveness of this classification system predicting histological outcome at surgery and its use defining appropriate management plans. This study seeks to show, for a cohort from a UK tertiary referral centre, if their rVC could have predicted residual cancer found at surgical resection and its relationship to survival rate.

OBJECTIVES

- To investigate the effectiveness of the rVC at predicting the presence of residual disease in surgical specimens after ER for upper GI dysplasia/early neoplasia a UK tertiary referral centre.
- To review whether the rVC at ER has any predictive value for survival.

METHODOLOGY

Retrospective data for all patients who had undergone ER for oesophageal or gastric lesions at Salford Royal NHS Foundation Trust, Salford, UK, between November 2011 and May 2018 were assessed for eligibility. This study was undertaken as part of the trust's routine service improvement and audit.

Inclusion

Eligible patients had a diagnosis pre-ER of a superficial lesion including squamous and glandular epithelial cell origin, oesophageal, gastro-oesophageal junction (GOJ) and gastric neoplasms. Lesions with low-grade dysplasia, high-grade dysplasia, invasive carcinoma limited to the submucosal layer classified as rVC ≤ 5 and staged at $\leq T1aN0M0$ based on CT or positron emission tomography-CT (PET-CT) scans and endoscopic ultrasound were selected.

Exclusion

Patients with lesions which were deemed to be unfit for ER, beyond submucosal invasion, staged at $\geq T1bN0M0$ or with lymph node or distant metastasis on PET scan or CT were excluded from the study.^{1 13}

Data sources/measurement

Detailed information regarding patient demographics, pre-ER and post-ER histopathology findings, surgery and endoscopic

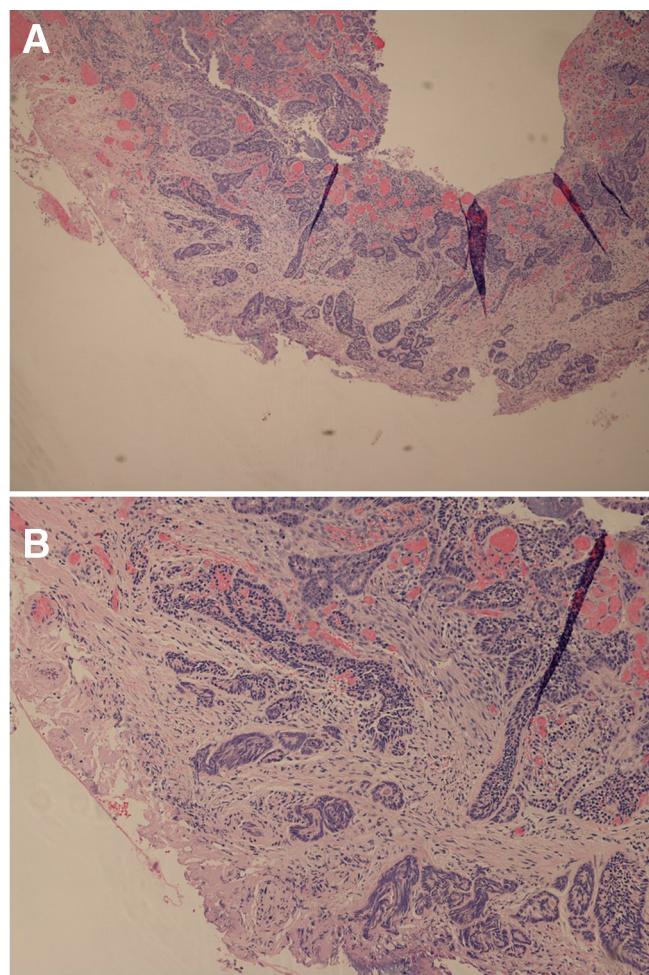


Figure 2 (A) H&E stained tissue section at $\times 4$ magnification demonstrating adenocarcinoma of intestinal type with extension into the submucosal compartment. The tumour is seen to extend to the deep resection margin of the specimen. (B) H&E stained section of the same specimen viewed at $\times 10$ magnification.

follow-up outcomes were gathered. The American Society of Anaesthetists (ASA) grades were used as a proxy marker of comorbid state when reviewing survival data. Multidisciplinary team (MDT) meeting and clinic letters, endoscopy and histopathological reports were retrieved from electronic patient records. Microsoft Excel software was used for data processing and statistical analysis.

Table 2 Patient characteristics included in the study, N (%)

Patient demographics	Value, n _p =157
Number of patients had ER, n	157
Age, mean \pm SD, year	70.9 \pm 10.4
Age, range, year	33–96
Gender, male	111 (70.7)
Gender, female	46 (29.3)
Ethnicity	
Caucasian	154 (98.1)
South Asian	3 (1.9)

ER, endoscopic resection.

Bias

To avoid bias, all patients who had completed an ER were reviewed for suitability. This was a retrospective study hence finding participants was dependent on coding accuracy; however, all patients undergoing ER were logged on a nationwide database, which meant there was stringent recording.

Sample size

The sample size was dependent on number of completed ERs and this was 195 lesions in 157 patients.

METHODS

All cases were initially referred for ER then decisions were made based on the histology if the ER specimen to proceed to surgical resection, surveillance or further ER. The techniques for ER are outlined in the 'Endoscopic resection technique' section.

Endoscopic resection technique

Initial mapping oesophagogastrroduodenoscopy was performed to review the lesion's size, position, macroscopic appearances and to evaluate the appropriateness of ER. The degree of lift from the submucosa after injection of lifting solution (Kato classification¹⁴) was assessed. Biopsies were taken for initial histological grading prior to ER.

The ERs were jointly performed by two interventional gastroenterologists experienced in ER. The ESD technique used in this centre has been described in detail in another paper by our group.⁷ The lesion was either removed en bloc, or a hybrid method was used whereby the lesion was demarcated with ESD creating a ridge, then hot snare resection en bloc was achieved with EMR. For the EMR lesions in the stomach, the lesion was lifted with EMR solution as above and snared with a mixed cutting and coagulation setting to remove the lesion en bloc or piecemeal. In the oesophagus, argon plasma coagulation was used to place dots 5 mm around the edge of the lesion, then a banding device was used to lift sections of the mucosa before removal with hot snare.

All the resected specimens were retrieved and pinned onto a specimen board, submerged in formalin solution and sent to the histopathology laboratory.

Surgical resections were performed under general anaesthetic by experienced upper GI surgeons at Salford Royal NHS Foundation Trust. Surgical specimens were retrieved and submerged in formalin solution prior to sending to the histopathology laboratory.

Histopathological evaluation and clinical management plan ER specimens

Endoscopically resected specimens were fixed in neutral buffered formaldehyde and processed into paraffin wax by standard histological methods; 3 μ m thick sections were cut and placed on twin frost slides (CellPath). Tissue sections were stained with H&E and reviewed by light microscopy by a histopathologist with a specialist GI interest to determine the differentiation grade and depth of invasion based on the rVC.¹³ The histological type, lymphovascular invasion, depth of invasion and horizontal and vertical margins were assessed in line with standard British criteria set by the Royal College of Pathologists 2007 datasets for histopathological reporting of gastric carcinoma and oesophageal carcinoma.¹⁵ Vascular markers (CD31, CD34) have been employed as an adjunct in our centre to confirm or exclude suspected foci of lymphovascular invasion. These antibodies stain both thin walled blood vessels and lymphatic channels. D2-40 staining is more specific and can be used to highlight lymphatic spaces alone but was not routinely used. The use of

vascular markers during the assessment of local resection specimens was not mandated in the UK at the time of the study. A resection specimen was coded complete resection (CR) if all margins were clear, non-CR if it failed to meet clear margins and indefinite if this was not established in the findings. Each specimen was reviewed in an MDT meeting including an experienced upper GI pathologist verifying the final rVC score.

Postsurgical specimens

Postsurgical specimens were processed as above. The evidence of dysplasia or neoplasia of each resected lesion was recorded and reported as the worst histological grade as per British standard reporting criteria.

Defining outcomes

The primary outcome of this study was to review how well the agreed histological grading using the rVC predicted the presence or otherwise of residual disease on surgical resected specimens.

The secondary end point was the overall survival rates of patients with rVC of category 4.4 and 5. Both patients who did not go on to have additional treatment and those who did were included in this subanalysis.

RESULTS

Patient demographics and features of lesions

One hundred fifty-seven patients with 195 lesions met inclusion criteria. The demographics of patients included are shown in table 2. Features of lesions excised by ER are summarised in table 3.

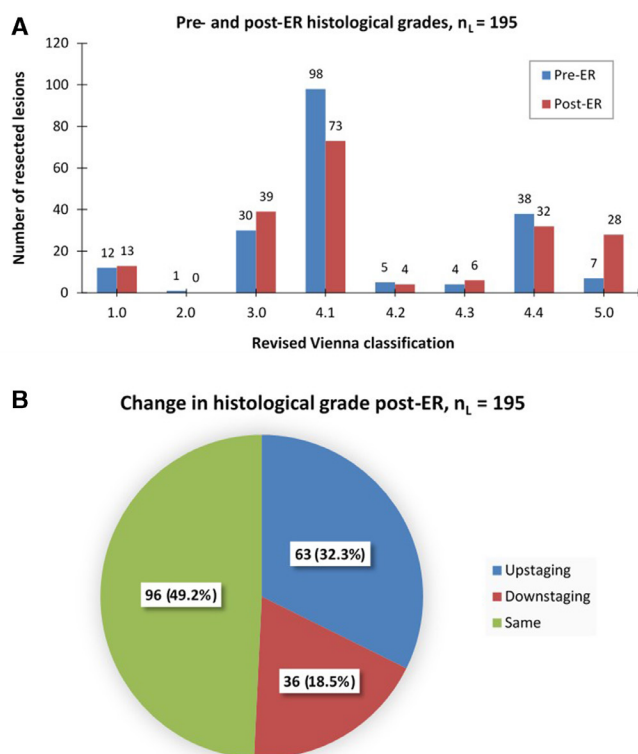


Figure 3 (A) Column chart showing the difference between pre-ER and post-ER histological grade based on the revised Vienna Classification for all 195 resected lesions. (B) A Pie chart showing how ER changed the histological grade of the resected lesions. ER, endoscopic resection; n_L, number of lesions.

Pre-ER and post-ER histological grade

Histological grade of 195 pre-ER and post-ER specimens from 157 patients were categorised based on the rVC (figure 3A), the rVC of lesions changed post-ER in 50.5% of specimens with 32.3% increasing in staging (figure 3B). Among the 195 resected specimens, 143 lesions (number of patients=113) were at least category 4.1. Hence, either a further ER or SR would be recommended to all these 113 patients (figure 4).

Post-ER clinical management plan

From the 113 patients (143 lesions) with category ≥ 4.1 , 10 of the patients (8.8%) had another session of ER. Forty-four patients (38.9%) were offered surgery, however, only 23 patients (20.4%)

Table 3 Features of lesions on which endoscopic resection has been attempted, N (%)

Location of lesion	Value, n _L =195	Lesions in which there was recurrence
Oesophagus	106 (54.4)	
Gastro-oesophageal junction	36 (18.5)	
Gastric	53 (27.1)	
Epithelial cell types of dysplasia or neoplasia	Value, n _L =195	
Glandular cell (adenocarcinoma)	178 (91.3)	
Squamous cell	17 (8.7)	
Macroscopic type (Paris Classification)	Value, n _L =195	
Ip, Isp	9 (4.6), 38 (19.5)	
Ila, Ilb, Ilc	63 (32.3), 12 (6.2), 1 (0.5)	
Isp/Ila, Ila/Ilb, Ila/Ilc	3 (1.5), 7 (3.6), 12 (6.2)	
Isp+Ila, Isp+Ilc	2 (1.0), 1 (0.5)	
Ila+Ilc, Ilc+Ila	40 (20.5), 1 (0.5)	
Ilb+Ilc	5 (2.6)	
III	1 (0.5)	
Size of lesion	Value, n _L =195	Value, n _L =55
≤ 30 mm	142 (72.8)	37 (67.3)
>30 mm	53 (27.2)	18 (32.7)
Differential type		
Clear of dysplasia/neoplasia	15 (7.6)	2 (4)
Low-grade/High-grade dysplasia only	114 (58.5)	31 (56)
Suspicious invasive	1 (0.5)	0 (0.0)
Well differentiated	30 (15.4)	11 (20)
Well to moderately differentiated	4 (2.1)	0 (0)
Moderately differentiated	18 (9.2)	6 (11)
Moderate to poorly differentiated	4 (2.1)	0 (0)
Poorly differentiated	9 (4.6)	5 (9)
Clearance of margin		
Vertical margin clear	69 (35.4)	20 (36.4)
Horizontal margin clear	57 (29.2)	13 (23.6)
Indefinite vertical margin clearance	72 (36.9)	20 (36.3)
Indefinite horizontal margin clearance	76 (39.0)	23 (41.8)
Vertical margin unclear	54 (27.7)	15 (27.3)
Horizontal margin unclear	62 (31.8)	19 (34.5)
Invasion		
Lymphovascular invasion	10 (5.1)	3 (5.5)
No lymphovascular invasion	185 (94.9)	52 (94.5)
Submucosal invasion >1 mm	29 (14.9)	9 (16.4)
No submucosal invasion >1 mm	166 (85.1)	46 (83.6)

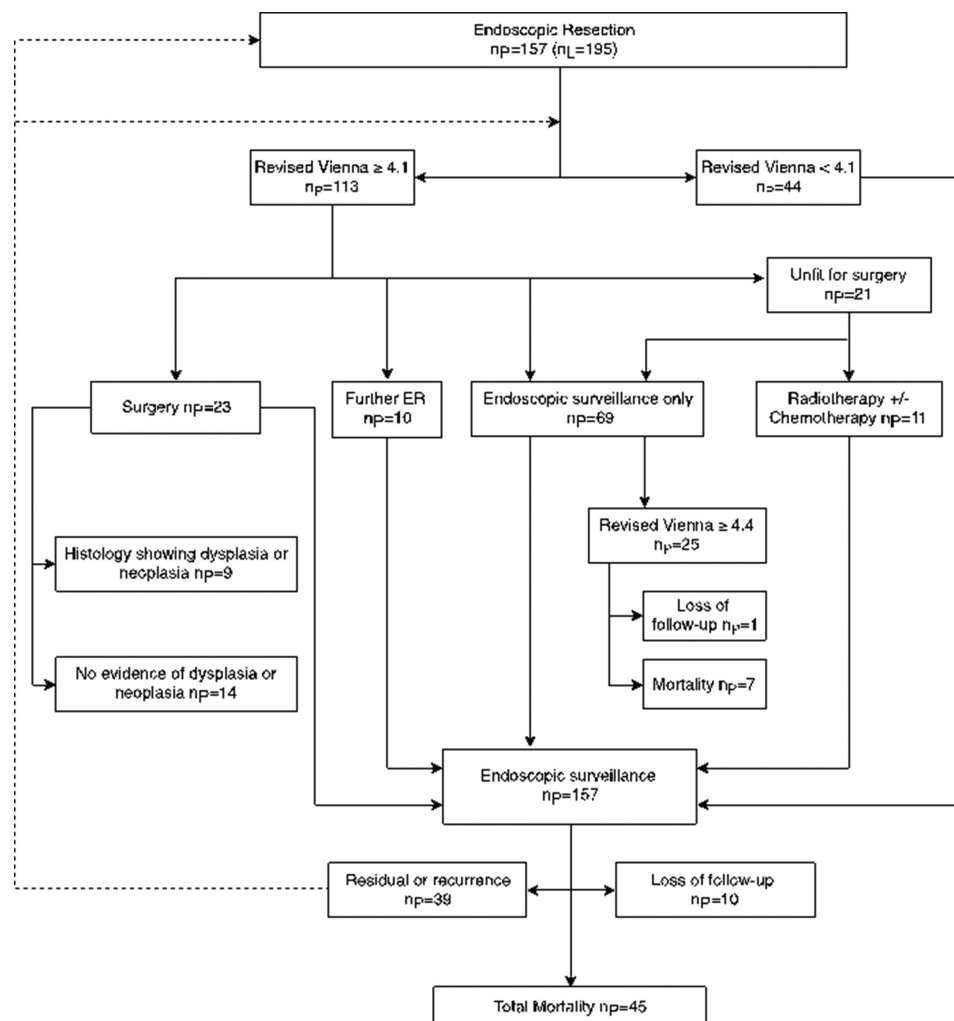


Figure 4 Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram illustrating clinical management pathway of patients with post-ER associated with their outcomes. ER, endoscopic resection; n_p =number of patients; n_l =number of lesions.

proceeded as 21 patients (18.6%) were deemed too unfit. Eleven of these patients (9.7%) were referred for radiotherapy with or without chemotherapy. The remaining 69 patients (61.1%) were either unfit or refused ER or surgery hence had endoscopic surveillance only (figures 4 and 5).

All the 157 patients were followed up with endoscopic surveillance. This includes the 44 patients with 52 resected lesions deemed category <4.1. During endoscopic follow-up, 39 out of 157 patients (24.8%) appeared to have either residual and/or recurrence as documented in table 4.

Postsurgery histological outcome

Fourteen out of 23 patients' SR specimens (60.9%) revealed no evidence of dysplasia/neoplasia on histology. In only nine patients' specimens (39.1%) were dysplastic or neoplastic cells associated with malignant potential identified (figure 5A). Eleven out of 14 lesions (78.6%) with no residual cancer detected were regarded as category 5 of the rVC at ER (figure 5B).

Overall survival rates of patients with Vienna ≥ 4.4 under endoscopic surveillance

Twenty-five out of 157 patients who were on endoscopic surveillance pathway were diagnosed with category 4.4 and 5. Among the 25 patients, 7 deaths were identified and 1 patient was lost to follow-up. The causes of death for all seven patients were

unrelated to their upper GI lesions. The mean and median age of deceased patients were 78.4 and 78 years, respectively. The overall mean survival time of all 25 patients was 39 months. The 7-year survival rate of 25 patients with category 4.4 and 5 was 68% (mean follow-up: 23.4 months, median follow-up: 23). The 7-year overall survival rate of category 4.4 was 73.6% (number of patients: 19, mean and median follow-up: 24.4 and 23 months). The 3-year overall survival rate of category 5 was 50% (number of patients: 6, mean and median follow-up: 20.2 and 21.5 months) (figure 6).

Postsurgical survival

For those with rVC of ≥ 4.4 , there was improved survival in those who had had surgical resection 92.3% vs 68% (figure 7). Likewise, in those who had rVC 5 there was a large difference (figure 8). As a proxy for comorbid state the age and ASA grades for each group were reviewed, for rVC ≥ 4.4 patients the median age for the surgical group was 65 years, with median ASA of 2, yet for the surveillance-only group the median age was 77 and ASA score of 3. Looking at the rVC 5 cases alone, the endoscopy surveillance group had median age of 77.6 and a median ASA grade of 3 compared with the rVC 5 surgery group whose median age was 64 and ASA grade of 2. Therefore, although the survival curves look in favour of surgical treatment, the data are confounded by differences in age and comorbid state.

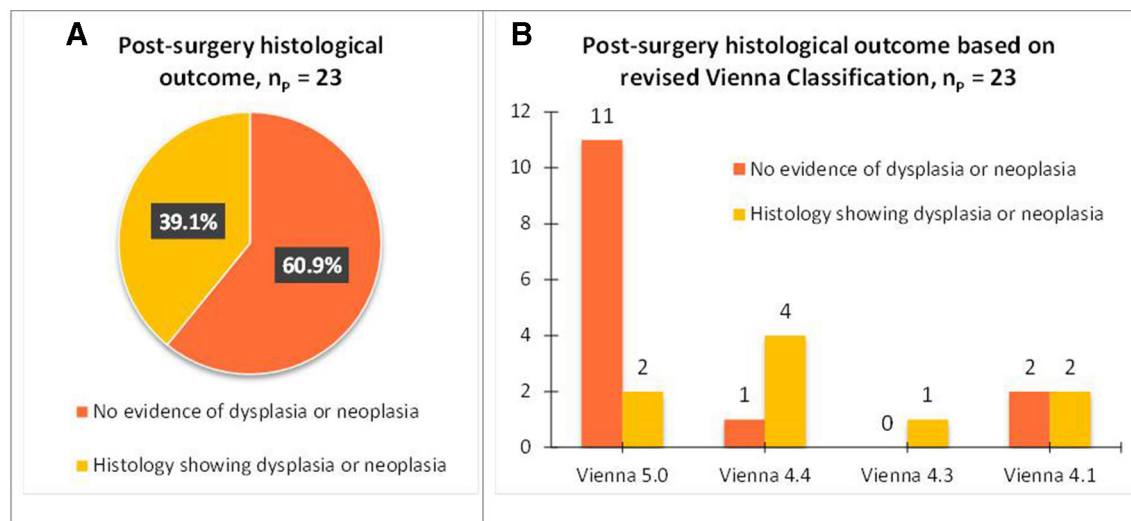


Figure 5 (A) Pie chart showing the rates of postsurgery histological outcome: histology shows dysplasia/neoplasia ($n_p=9$) and no evidence of dysplasia/neoplasia ($n_p=14$). (B) Column chart comparing the previous post-ER histological outcomes of 23 surgically resected specimens based on the revised Vienna Classification: category 5 ($n_p=11$ vs $n_p=2$), category 4.4 ($n_p=1$ vs $n_p=4$), category 4.3 ($n_p=0$ vs $n_p=1$) and category 4.1 ($n_p=2$ vs $n_p=2$). ER, endoscopic resection; n_p , number of patients.

DISCUSSION

The effectiveness of the rVC at predicting post-ER histological outcome has been investigated in this study. Despite careful selection for ER, some lesions require surgery post-ER as they fail to meet the curative criteria defined by the JES/JGCA guidelines^{8–10} or are classified category >4 in the rVC.⁴ Despite this our primary outcome demonstrated most SR specimens (14/23, 60.9%) contained no histological evidence of residual dysplasia/neoplasia. Our result is consistent with Tate *et al*,¹⁶ Sunagawa *et al*¹⁷ and Koide *et al*,¹⁸ who found similar or even more positive findings of 70%–94.4%. Among 14 specimens with no residual cancer detected, 11 of them (78.6%) were classified as category 5 of rVC whereas for Tate *et al*¹⁶ only 40% of their postoperative gastric specimens without residual tumour were equivalent to category 5. Nakata *et al*¹⁹ reported up to 50% of their SR specimens harboured residual cancer. Even so, these specimens were at least SM2 (submucosal invasion $>500\mu\text{m}$ from muscularis mucosae) and had lymphatic involvement. Both factors indicate a greater level of invasiveness which ER alone would not suffice as a definitive cure. In short, there may be further variation in the natural history of rVC 5 lesions—a subcategory which is more likely to demonstrate dysplasia at surgical resection and had deeper invasion at initial ER. These findings suggest there may be some merit in further defining the level of rVC 5 lesions to better risk stratify patients to surgery. Unnecessary referral for surgery should be avoided as it carries significant morbidity

and mortality.^{2–4 20 21} Based on the National Oesophago-gastric Cancer Audit 2017, 36.4% of patients reported suffering with complications caused by oesophagectomy and 21.7% after gastrectomy. Notably, there was a 90-day postoperative mortality rate of 3.3% in oesophagectomy and 3.1% in gastrectomy.²¹

In this study, 69 patients chose to have endoscopic surveillance only. Twenty-five patients from this cohort (39.9%) had lesions graded ≥ 4.4 of the rVC (at least intramucosal carcinoma). The 7-year overall survival rate of category ≥ 4.4 was 68%, with 73.6% specifically to category 4.4 (intramucosal carcinoma) alone. Our secondary outcome was supported by the 5-year overall survival rates of Toya *et al*²² and Jeon *et al*,²³ which were 76.2% and 86.2%, respectively. However, our patients with category 5 (submucosal carcinoma) only achieved a 3-year overall survival rate of 50%, which could be explained by our small sample size making the comparison less justifiable. More importantly, there were marked differences in age and comorbid state between the groups in favour of the surgically treated group yet none of the mortality was disease-related. Overall, our survival rates were comparable to reported oesophagectomy and gastrectomy survival rates of 46%–89.7%.^{24 25} In essence, this could imply that endoscopic surveillance and symptomatic control may be all that is needed for elderly patients with category ≥ 4.4 of the rVC after ER for early gastro-oesophageal lesions.

The main rationale of overtreating patients is due to concern regarding the poor outcomes for invasive upper GI malignancy, but may be compounded by the ambiguity of category 5 in the rVC. Schlemper and Iwashita¹ mentioned that additional SR is only required for superficial submucosal carcinoma when it is poorly differentiated with lymphovascular invasion. However, the rVC category 5 includes all carcinomas with invasion into submucosal layer or beyond.¹ As suggested by the European Society of Gastrointestinal Endoscopy (ESGE) guideline, the depth of submucosal invasion can be classified as upper third (SM1), middle third (SM2) or lower third (SM3) invasion in accordance with Japanese guidelines (JGCA¹⁰ and JES^{8 9}). Although submucosal invasion can only be correctly estimated in post-SR specimens rather than ER, a maximum depth of submucosal invasion could be adopted. In oesophageal squamous cell cancer, SM1 invasion is defined as the superficial portion of

Table 4 Residual and recurrence, N (%)

Types of recurrence	Value, $n_p=39$
Residual only	14 (35.9)
Local recurrence only	15 (38.4)
Synchronous recurrence only	1 (2.6)
Metachronous only	3 (7.7)
Mixed recurrences	
Residual and local recurrence	2 (5.1)
Residual and synchronous recurrence	1 (2.6)
Local and metachronous recurrence	3 (7.7)

None of the postsurgery patients showed residual or recurrent disease.

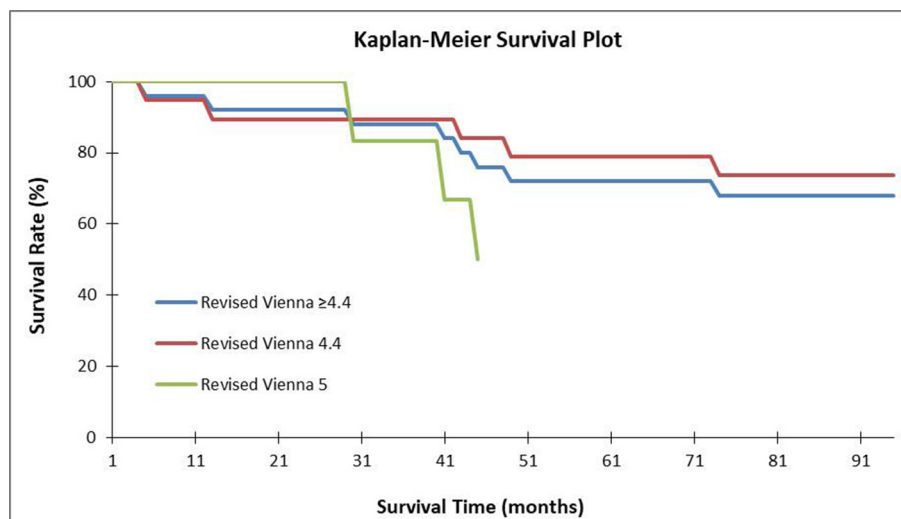


Figure 6 Kaplan-Meier survival curves: 25 patients with category ≥ 4.4 (blue); 19 out of 25 patients with category 4.4 (red) and 6 patients with category 5 (green). These patients were on endoscopic surveillance only.

submucosa measured $\leq 200 \mu\text{m}$ from the bottom fibre of muscularis mucosae. In gastric carcinoma, SM1 is restricted to invasion at $\leq 500 \mu\text{m}$ instead.^{2 8–10} In Barrett's lesions, this may be difficult however, as in Barrett's metaplasia the muscularis mucosa can be duplicated making the boundary of the mucosa/submucosa difficult to define.²⁶ Postsurgical specimen studies looking at SM levels of oesophageal adenocarcinomas have shown unacceptable risk of lymphovascular spread for all levels hence subdivision of the SM may not be feasible in this group.^{27 28}

Unfortunately, the depths of submucosal invasion of post-ER specimens were not specified in this study. Notwithstanding our limitation, we still highly recommend that the category 5 of rVC to be refined and expanded by incorporating a clear distinction of the depth of submucosal invasion and lymphovascular involvement as suggested by the ESGE, JGCA and JES guidelines.^{2 8–10} This has been acknowledged in the new Royal College of Pathologists UK Dataset for histopathological reporting of oesophageal and gastric carcinoma which was published in October 2019 after this study was completed.²⁹ Further work is required to see

if this subclassification can accurately predict who is more likely to have residual disease at resection.

Limitations

The main limitation of this study includes a potential selection bias as the study involved a single-centre recruitment of 98.1% Caucasian patients. However, this is a long-term retrospective study on well-characterised cases from a Western tertiary referral centre. Little work has been done to look at outcomes in this population group with most work focusing on Asian populations and hence this work adds a valuable insight into the Western population.

Conclusion

In conclusion, our study demonstrated that there is a cohort of patients whose ER specimens meet the criteria of the category 5 of the rVC that may not have necessarily required further surgery. These patients may benefit from having endoscopic

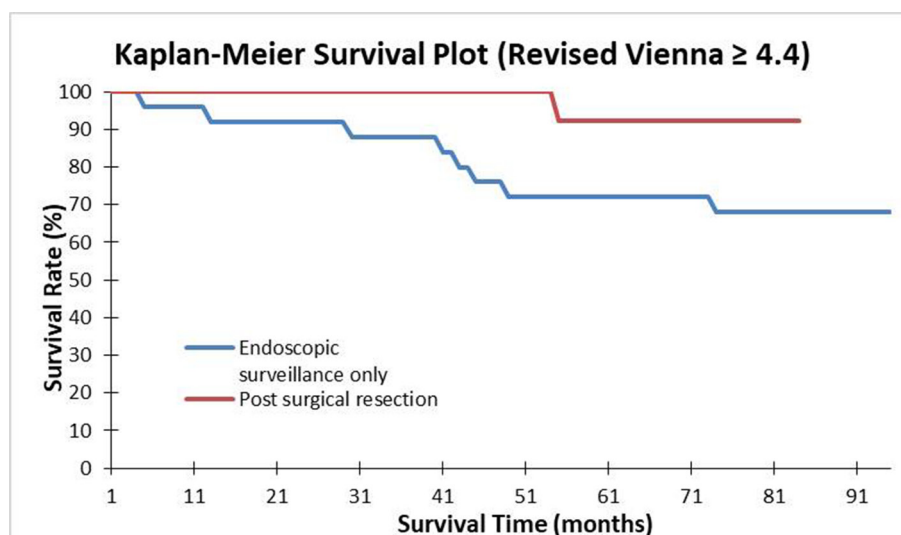


Figure 7 Kaplan-Meier survival curves: 43 patients with category ≥ 4.4 ; 18 out of 25 patients on endoscopic surveillance alone (blue) and 17 out of 18 patients who had surgery (red); 1 is missing purely due to lost to follow-up uncertain of outcome.

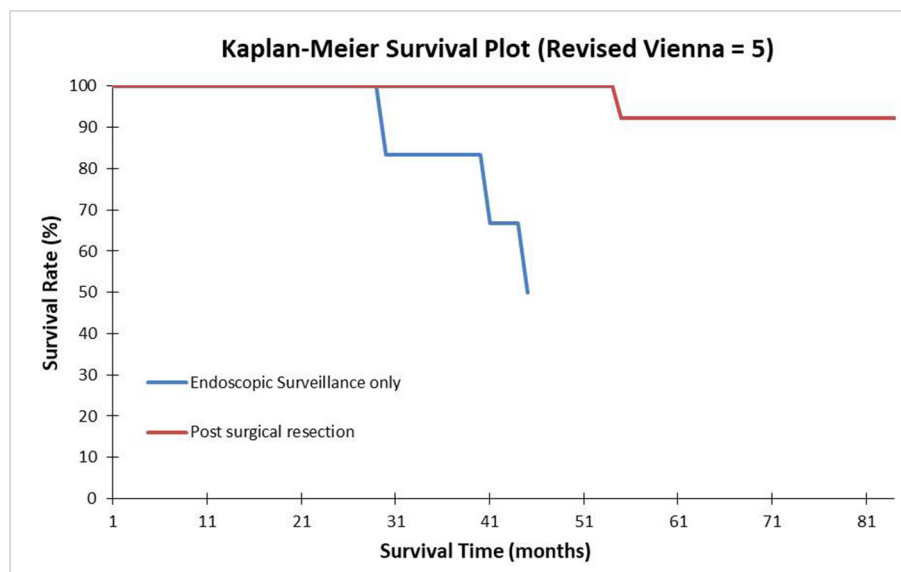


Figure 8 Kaplan-Meier survival curve: 19 patients with category 5; 3 out of 6 patients on endoscopic surveillance alone (blue) 3-year survival. Seventeen out of 18 patients who had surgery (red) 7-year survival; 1 patient is missing due to being lost to follow-up hence uncertain of outcome rather than died.

surveillance alone. To avoid overtreatment, the category 5 of the rVC needs further evaluation and refinement by expanding into subcategories for different depths of submucosal invasion. Future research could look at applying the refined category 5 of the rVC in a large multicentre Western and Japanese prospective study to test its effectiveness at predicting histopathological outcomes and defining clinical management. The purpose of improving the rVC is to increase its potential in facilitating better patient care and international comparability of early gastro-oesophageal cancers.

Take home messages

- The revised Vienna Classification (rVC) is a useful tool to help judge which upper gastrointestinal neoplastic lesions require further treatment.
- Our study shows high proportion of cases deemed rVC 5, which showed no residual tumour cells after surgery (60.9%).
- This supports the move to subcategorise the submucosal level of invasion, which may help in preventing unnecessary surgery in this often older demographic.

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Contributors JK: performed data collection, analysis and prepared an early draft of the manuscript. ER: performed further analysis of the data, was responsible for rewriting, editing and revising the manuscript after the initial draft. SH and SMcG: provided histopathology expertise during the project and writing of the manuscript. They reviewed the specimens and provided the images for figures 1 and 2. YA: conceived the project, had overall responsibility for the publication. All authors contributed to and reviewed the final drafts of the paper prior to submission.

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REFERENCES

- Schlemper RJ, Iwashita A. Classification of gastrointestinal epithelial neoplasia. *Current Diagnostic Pathology* 2004;10:128–39.
- Pimentel-Nunes P, Dinis-Ribeiro M, Ponchon T, *et al.* Endoscopic submucosal dissection: European Society of gastrointestinal endoscopy (ESGE) guideline. *Endoscopy* 2015;47:829–54.
- Ning B, Abdelfatah MM, Othma MO. Endoscopic submucosal dissection and endoscopic mucosal resection for early stage esophageal cancer. *Ann. Cardiothorac. Surg.* 2017;6:88–98.
- Kandiah K, Chedgy FJQ, Subramaniam S, *et al.* Early squamous neoplasia of the esophagus: the endoscopic approach to diagnosis and management. *Saudi J Gastroenterol* 2017;23:75–81.
- Kanzaki H, Ishihara R, Ohta T, *et al.* Randomized study of two endo-knives for endoscopic submucosal dissection of esophageal cancer. *Am J Gastroenterol* 2013;108:1293–8.
- Kim JS, Kim B-W, Shin I-S. Efficacy and safety of endoscopic submucosal dissection for superficial squamous esophageal neoplasia: a meta-analysis. *Dig Dis Sci* 2014;59:1862–9.
- Sooltongos A, Davenport M, McGrath S, *et al.* Gastric endoscopic submucosal dissection as a treatment for early neoplasia and for accurate staging of early cancers in a United Kingdom Caucasian population. *World J Gastrointest Endosc* 2017;9:561–70.
- Matsubara H, Ando N, Nemoto K, *et al.* Japanese classification of esophageal cancer, 11th edition: Part I. *Esophagus* 2017;14:1–36.
- Matsubara H, Ando N, Nemoto K, *et al.* Japanese classification of esophageal cancer, 11th edition: Part II and III. *Esophagus* 2017;14:37–65.
- Sano T, Kodera Y. Japanese gastric cancer treatment guidelines 2010 (VER. 3). *Gastric Cancer* 2011.
- Kim EH, Park JC, Song JJ, *et al.* Prediction model for non-curative resection of endoscopic submucosal dissection in patients with early gastric cancer. *Gastrointest Endosc* 2017;85:976–83.
- Schlemper RJ *et al.* The Vienna classification of gastrointestinal epithelial neoplasia. *Gut* 2000;47:251–5.
- Dixon MF. Gastrointestinal epithelial neoplasia: Vienna revisited. *Gut* 2002;51:130–1.
- Kato H, Haga S, Endo S, *et al.* Lifting of lesions during endoscopic mucosal resection (EMR) of early colorectal cancer: implications for the assessment of resectability. *Endoscopy* 2001;33:568–73.

- 15 Novelli M, Working Group on Cancer Services. *Dataset for the histopathological reporting of gastric carcinoma*. 2nd edn, 2007. <https://www.rcpath.org/uploads/assets/d424aaee-6170-4171-ba184326229af027/Dataset-for-the-histopathological-reporting-of-gastric-carcinoma.pdf>
- 16 Tate DJ, Klein A, Sidhu M, *et al*. Endoscopic submucosal dissection for suspected early gastric cancer: absolute versus expanded criteria in a large Western cohort (with video). *Gastrointest Endosc* 2019.
- 17 Sunagawa H, Kinoshita T, Kaito A, *et al*. Additional surgery for non-curative resection after endoscopic submucosal dissection for gastric cancer: a retrospective analysis of 200 cases. *Surg Today* 2017;47:202–9.
- 18 Koide N, Takeuchi D, Suzuki A, *et al*. Additional gastrectomy after endoscopic submucosal dissection for early gastric cancer patients with comorbidities. *Int J Surg Oncol* 2012;2012:1–7.
- 19 Nakata B, Tendo M, Okuyama M, *et al*. Additional surgical resection after endoscopic mucosal dissection for early gastric cancer: a medium-sized hospital's experience. *Int J Surg* 2016;36:335–41.
- 20 Yip H-C, Chiu PW-Y. Endoscopic diagnosis and management of early squamous cell carcinoma of esophagus. *J Thorac Dis* 2017;9:S689–96.
- 21 Maynard M, Chadwick G, Varagunam M, *et al*. National oesophago-gastric cancer audit 2017. *R Coll Surg Engl* 2017;10–24.
- 22 Toya Y, Endo M, Nakamura S, *et al*. Clinical outcomes of non-curative endoscopic submucosal dissection with negative resected margins for gastric cancer. *Gastrointest Endosc* 2017;85:1218–24.
- 23 Jeon MY, Park JC, Hahn KY, *et al*. Long-term outcomes after noncurative endoscopic resection of early gastric cancer: the optimal time for additional endoscopic treatment. *Gastrointest Endosc* 2018;87:1003–13.
- 24 Tachibana M, Kinugasa S, Shibakita M, *et al*. Surgical treatment of superficial esophageal cancer. *Langenbecks Arch Surg* 2006;391:304–21.
- 25 Chiu PWY, Teoh AYB, To KF, *et al*. Endoscopic submucosal dissection (ESD) compared with gastrectomy for treatment of early gastric neoplasia: a retrospective cohort study. *Surg Endosc* 2012;26:3584–91.
- 26 Abraham SC, Krasinskas AM, Correa AM, *et al*. Duplication of the muscularis mucosae in Barrett esophagus: an underrecognized feature and its implication for staging of adenocarcinoma. *Am J Surg Pathol* 2007;31:1719–25.
- 27 Leers JM, DeMeester SR, Oezcelik A, *et al*. The prevalence of lymph node metastases in patients with T1 esophageal adenocarcinoma: a retrospective review of esophagectomy specimens. *Ann Surg* 2011;253:271–8.
- 28 Sepesi B, Watson TJ, Zhou D, *et al*. Are endoscopic therapies appropriate for superficial submucosal esophageal adenocarcinoma? an analysis of esophagectomy specimens. *J Am Coll Surg* 2010;210:418–27.

68f1e8eb-1d40-4741-b9ca-809825d38b55 Grabsch H, Mapstone N, Novelli M. *Standards and datasets for reporting cancers dataset for histopathological reporting of oesophageal and gastric carcinoma*. London UK: Royal College of Pathologists, 2019: 1–58. <https://www.rcpath.org/uploads/assets/f8b1ea3d-5529-4f85-984c8d4d8556e0b7/g006-dataset-for-histopathological-reporting-of-oesophageal-and-gastric-carcinoma.pdf>