NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of endoscopic submucosal dissection of gastric lesions

This procedure can be used to treat abnormalities on the wall of the stomach. A long camera (endoscope) is inserted through the oesophagus and into the stomach to view the affected area. A solution is injected into the wall of the stomach, and then the part of the stomach wall that looks abnormal is removed with special instruments. The aim of the procedure is to help avoid the need for open surgery, and to obtain a good quality sample for examination under the microscope.

Introduction

The National Institute for Health and Clinical Excellence (NICE) has prepared this overview to help members of the Interventional Procedures Advisory Committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in March 2010.

Procedure name

- Endoscopic submucosal dissection of gastric lesions

Specialty societies

- British Society of Gastroenterology

- The Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland

- The Association of Laparoscopic Surgeons of Great Britain and Ireland.

Description

Indications and current treatment

'Gastric lesions' may include benign (hamartomatous), adenomatous (dysplastic) lesions, and malignant (adenocarcinoma, or, more rarely, carcinoid) tumours. Many patients with gastric lesions may be asymptomatic, but some patients may experience loss of appetite and unexplained weight loss, anaemia and abdominal discomfort or pain.

Lesions are usually identified and investigated endoscopically, but sometimes radiological means are used (such as a barium meal). If these tests are positive, further tests such as computed tomography (CT), endoscopic ultrasound or magnetic resonance imaging (MRI) may also be used. Treatment will depend on the clinical presentation and symptom status and usually involves surgery, chemotherapy or both; and sometimes involves radiotherapy.

Depending on their type, current practice for the management of small gastric lesions usually involves snare polypectomy (for lesions protruding into the bowel lumen) or endoscopic mucosal resection (EMR) (for laterally spreading or 'flat' lesions). EMR involves injection of a solution (usually sodium hyaluronate) into the submucosal layer underneath the lesion in order to raise it and ease its piecemeal removal using a snare. Histological diagnosis can be confirmed before endoscopic treatment, but in practice small lesions may also be removed endoscopically – without confirmation as to whether they are malignant or benign and before a biopsy result. The aim of EMR is to both remove and diagnose the lesion.

Lesion stage and morphology classifications

In the relevant literature, the histological stage of upper gastrointestinal lesions can be classified as follows:

- m1 – intraepithelial carcinoma

- m2 – microinvasive carcinoma (invasion through the basement membrane)

- m3 – intramucosal carcinoma (invasion to the muscularis mucosae)

- sm1 – superficial invasion in the submucosa (less than 200 micrometres below the muscularis mucosae)

- sm2 or sm3 – middle invasion in the submucosa (more than 200 micrometres below the muscularis mucosae).

For lesions morphology, a commonly used classification scheme is the Paris system. Polypoid lesions (protruding into the lumen) are classified as 0-I (Ip, Ips or Is, depending on whether or not they are pedunculated, subpedunculated or sessile). Non-polypoid lesions are classified as 0-IIa if they are slightly elevated, 0-IIb if they are flat without elevation or depression,

and 0-IIc if they have central mucosal depression. Combination categories also exist, e.g. 0–IIc and IIa for lesion have mucosal depression with an elevated edge. Ulcerated lesions are characterised as 0-III.

The relevant literature also refers to Japanese Gastric Cancer Association (JGCA) guidelines, which originally recommended that only lesions less than 20 mm should be dissected endoscopically (otherwise radical surgery should be performed). This criterion was expanded when endoscopic submucosal dissection was introduced to include lesions of any size for differentiated mucosal cancer without ulceration, and less than 30 mm if ulceration was present.

The residual tumour classification system is often used to denote completeness of surgical resection. R0 denotes a complete resection with both lateral and basal margins free, R1 denotes incomplete resection (either at lateral or basal margins). Rx denotes margins that are not evaluable because of necrosis or a piecemeal resection.

What the procedure involves

Endoscopic submucosal dissection (ESD) is a modification of EMR. In ESD, a specially designed electrocautery knife is used to resect the lesion in one piece (en bloc) without the use of a snare. This aims to permit a more accurate histopathological assessment and decrease the risk of recurrence.

Diagnostic endoscopy, biopsy and imaging investigations are often carried out before the procedure. The procedure is usually performed with the patient under sedation or general anaesthesia. Substances to inhibit peristalsis (such as hyoscine or glucagon) may be administered intravenously before the procedure. The submucosa is injected with fluid that may contain sodium hyaluronate. This lifts the lesion off the submucosa, making the lesion protrude into the gastric lumen. Small quantities of a pigment dye may be included in the submucosal injection to help define the edge of the lesion, and adrenaline may be included to reduce the risk of bleeding.

An initial circumferential mucosal incision is made with the electrocautery knife around the lesion. Submucosal dissection is then performed under direct vision, parallel to the muscle layer, aiming to remove the lesion intact en bloc and with a healthy margin of tissue. A transparent hood may be used to retract the already dissected part of the lesion out of the field of view. The electrocautery knife is used to achieve haemostasis. Endoscopic clips may be used for larger vessels or to manage perforation.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to endoscopic submucosal dissection of gastric lesions. Searches were conducted of the following databases, covering the period from their

commencement to 19 May 2010: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies.
	Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study.
	Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with gastric lesions.
Intervention/test	Endoscopic submucosal dissection.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the overview

This overview is based on about 3037 patients from 5 non-randomised comparative studies, 2 case series and 4 case reports.

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Table 2 Summary of key efficacy and safety findings on endoscopic submucosal dissection of gastric lesions

Abbreviations used: APC, argon plasma coagulation; CT, computed topography; EGC, early gastric cancer; EGD, esophagogastroduodenoscopy; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; EUS, endoscopic ultrasound; GIST, gastro-intestinal stromal tumour; IMC, intramucosal cancer; JGCA, Japanese Gastric Cancer Association; M, mucosal; R0, en-bloc resection with tumour-free margins; R1, en-bloc resection without tumour-free margins; sm, submucosal; sm1, superficial invasion in the submucosa (less than 200 micrometres below the muscularis mucosae

Study details	Key efficacy findings	Key safety findings	Comments
Hoteya S (2009)[1] **Non-randomised comparative study** Japan Recruitment period: 2000–2005 (EMR), 2005–2007 (ESD) Study population: EGC without vestigial remnant or recurrence n = **900 lesions (572 ESD vs 328 EMR)** **Mean age**: 67.9 years (ESD), 67.8 years (EMR) **Sex**: 77% male (ESD), 82% male (EMR) **Location**: ESD – upper third (117), middle third (267), lower third (188), EMR – upper third (50), middle third (134), lower third (144) **Depth**: not reported **Mean size**: 21.3 mm (ESD), 11.8 mm (EMR) Patient selection criteria: IMC (if ulceration present, must be less than 3 cm in diameter), minimally invasive submucosal cancer (invasion < 500 from muscularis mucosa with no lymph invasion, adenoma with potential for malignancy) Exclusion criteria: previous upper gastrointestinal surgery Technique: EMR using either 2-channel endoscope or a transparent cap and ESD with patient usually under conscious sedation (sometimes general anaesthetic was used)	Number of patients analysed: **900 lesions (572 ESD vs 328 EMR)** ***Completeness of resection*** |	ESD	EMR	 | ---	---	---	 | Complete resection rate	95.1% (544/572)	64.0% (210/328)*	 | Curative resection rate	82.7% (473/572)	59.5% (195/328)	 (p < 0.05 for both regardless of location except in lesions less than 5 mm in diameter where it was not significantly different) *this figure was incorrectly reported in the study as 64.2%. ***Local recurrence*** No recurrences in ESD group during follow-up. Recurrences were 4% (13/328) in EMR group (time of follow-up not reported; p < 0.05). No details about these recurrences were provided.	***Complications*** |	ESD	EMR	 | ---	---	---	 | Postoperative bleeding	4.9% (28/572)	5.2% (17/328)	 | Perforation	3.5% (20/572)	1.5% (5/328)	 (these were not significantly different) No more details of the complications (such as how they were treated) were provided.	**Follow-up issues**: • Endoscopy performed at 2, 6 and 12 months. **Study design issues**: • This study reported outcomes before and after the introduction of ESD at one centre, when the JGCA indications expanded to include larger lesions. **Study population issues**: • Lesions were significantly smaller in the EMR group. • Number of patients (with 900 lesions) treated not reported. **Other issues**: • All patients had endoscopy and were biopsied before inclusion in the study. • While the aim of the study was to look at early gastric cancer,

Abbreviations used: APC, argon plasma coagulation; CT, computed topography; EGC, early gastric cancer; EGD, esophagogastroduodenoscopy; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; EUS, endoscopic ultrasound; GIST, gastro-intestinal stromal tumour; IMC, intramucosal cancer; JGCA, Japanese Gastric Cancer Association; M, mucosal; R0, en-bloc resection with tumour-free margins; R1, en-bloc resection without tumour-free margins; sm, submucosal; sm1, superficial invasion in the submucosa (less than 200 micrometres below the muscularis mucosae

Study details	Key efficacy findings	Key safety findings	Comments
Follow-up: **not reported** Conflict of interest/source of funding: not reported			adenomas that were potentially malignant were included. It was not known if any patients included were in this category.

Abbreviations used: APC, argon plasma coagulation; CT, computed topography; EGC, early gastric cancer; EGD, esophagogastroduodenoscopy; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; EUS, endoscopic ultrasound; GIST, gastro-intestinal stromal tumour; IMC, intramucosal cancer; JGCA, Japanese Gastric Cancer Association; M, mucosal; R0, en-bloc resection with tumour-free margins; R1, en-bloc resection without tumour-free margins; sm, submucosal; sm1, superficial invasion in the submucosa (less than 200 micrometres below the muscularis mucosae

Study details	Key efficacy findings	Key safety findings	Comments
Oka S (2006)[2] **Non-randomised comparative study** Japan Recruitment period: 1990–2002 (EMR), 2002–2004 (ESD), Study population: EGC n = **896 (195 ESD vs 811 EMR) (1020 lesions: 195 ESD vs 825 EMR)** **Mean age**: not reported **Sex**: not reported **Location**: ESD – upper third (34), middle third (97), lower third (64), EMR – upper third (188), middle third (294), lower third (343) **Depth**: ESD – m (173), sm (22), EMR – m (776), sm (49) **Mean size**: ESD – ≤ 10 mm (46), 11–20 mm (100), ≥ 21 mm (49), EMR – ≤ 10 mm (424), 11–20 mm (294), ≥ 21 mm (107) **Presence of ulceration**: ESD – 13.3% (26/195), EMR – 4.2% (35/825) Patient selection criteria: not reported Technique: EMR with 2-channel endoscopy or single channel endoscope (later margin 'trimmed' with heat probe or APC after EMR) and ESD Maximum follow-up: **28.6 months (ESD) and 117.8 months (EMR)**	Number of patients analysed: **896 (195 ESD vs 811 EMR) (1020 lesions: 195 ESD vs 825 EMR)** *Completeness of resection* Complete resection rate is the histological resection rate (histologically clear margins) En-bloc resection rate / Complete resection rate (see below table) *p < 0.01 (overall ESD vs EMR; still significant when calculated in subgroups by lesion size) ** p < 0.05 (overall ESD vs EMR; when calculated in subgroups by lesion size, the differences were not significant) (It is not clear if ulceration was determined at baseline or with the endoscope at the time of the procedure.) *Reasons for incomplete resection:*	*Complications:* (see below table) *p < 0.01 ** The incorrect denominator was used for this outcome in this study, so the rate has been recalculated by the analyst. *Bleeding* All cases of bleeding were successfully controlled with endoscopic treatment (electrocoagulation or haemoclipping).	**Follow-up issues**: • Endoscopy for local recurrence performed at 12 months and then every 12 months for complete resections and at 3 months and then every 12 months for incomplete resections. • There appear to be a loss to follow-up 9 lesions follow-up for recurrences but this was not explained. **Study design issues**: • This is a retrospective study reported outcomes before and after the introduction of ESD at one centre when the indications in the JGCA guidelines were expanded to include larger lesions (exact size not stated). **Study population issues**: • Patients treated with ESD had significantly larger lesions, more IIc

Efficacy table:

	ESD	EMR
En-bloc resection rate:		
Lesions without ulceration*	92.9% (157/169)	43.4% (343/790)
Ulcerated lesions	19.2% (5/26)	11.4 % (4/35)
Complete resection rate:		
Lesions without ulceration*	92.9% (157/169)	24.6% (194/790)
Ulcerated lesions**	19.2 % (5/26)	2.9% (1/35)

Safety table:

	ESD	EMR
Perforation rate:		
Lesions without ulceration*,**	11.2% (19/169)	0.5% (4/790)
Ulcerated lesions	1.2% (2/169)	0.3% (3/790)
Intraoperative bleeding rate:		
Lesions without ulceration*	22.6% (44/195)	7.6% (63/825)
Ulcerated lesions*	23.1% (39/169)	7.0% (55/790)
Postoperative bleeding rate:		
Lesions without ulceration	6.2% (12/195)	3.9% (32/825)
Ulcerated lesions	5.9% (10/169)	3.3% (26/790)

Abbreviations used: APC, argon plasma coagulation; CT, computed topography; EGC, early gastric cancer; EGD, esophagogastroduodenoscopy; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; EUS, endoscopic ultrasound; GIST, gastro-intestinal stromal tumour; IMC, intramucosal cancer; JGCA, Japanese Gastric Cancer Association; M, mucosal; R0, en-bloc resection with tumour-free margins; R1, en-bloc resection without tumour-free margins; sm, submucosal; sm1, superficial invasion in the submucosa (less than 200 micrometres below the muscularis mucosae

Study details	Key efficacy findings	Key safety findings	Comments
Conflict of interest/source of funding: none	ESD: perforation (33.3%, 11/33), inability to stop bleeding during procedure (18.2%, 6/33), ulceration (39.4%, 13/33), technical difficulty (in controlling the scope or another device (9.1%, 3/33). EMR: tumour size (22.6%, 108/478), tumour location (47.3%, 226/478), ulceration (4.4%, 21/478), technical difficulty (25.7%, 123/478) ***Local recurrence rates*** Overall local recurrence rate was 3.1% (31/1011) at a mean follow-up of 19.4 months (ESD group) and 83.2 months (EMR group).	Blood transfusion was required in 2 cases in the EMR group without ulceration and 1 case with ulceration in the ESD group. ***Perforation*** While the table in the study reports that there were 21 perforations in the ESD group, the text reports that there were 13 perforations in this group. If there were 13 perforations, the overall perforation rate would be 6.7% in the ESD group. The author also states that there were 4 perforations in the EMR group, but the table has 7 cases of perforation (as above).The reason for this is unknown.	and IIa and 11c lesions, deeper lesions with proportionately more patients with ulceration. The histological type of tumours were also significantly different (see first column) but there was no significant difference in location of the lesion. • There were no lesions less than 4mm. **Other issues**: • Prediagnosis with endoscopic observation and EUS was performed to confirm the depth. • Rates of perforation were inconsistently reported in the table and text of the study (see safety column).

	ESD	EMR
Patients with en-bloc resection	0% (0/62)	2.9% (10/347)
Patients with piecemeal resection	0% (0/33)	4.4% (21/478)

All local recurrences were treated with additional endoscopic treatment or surgery.

Operation time

This was significantly longer for ESD than EMR, regardless of tumour size (84.4 ± 55.3 minutes vs 12.6 ±9.3 minutes; $p < 0.01$).

Even in lesions less than 10mm, it took 58.5 ± 28.7 minutes to perform ESD.

The author states that 4 of the 13 patients with perforation required open surgery. The others (and those in the EMR group with perforation) were successfully treated with endoscopic clipping, intubation with a nasogastric tube, discontinuation of oral intake and intravenous administration of antibiotics.

They also state that 10 of the 13 cases of perforation in the ESD group were within 12 months of the introduction of the technique for this indication.

There were no cancer-related deaths.

Abbreviations used: APC, argon plasma coagulation; CT, computed topography; EGC, early gastric cancer; EGD, esophagogastroduodenoscopy; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; EUS, endoscopic ultrasound; GIST, gastro-intestinal stromal tumour; IMC, intramucosal cancer; JGCA, Japanese Gastric Cancer Association; M, mucosal; R0, en-bloc resection with tumour-free margins; R1, en-bloc resection without tumour-free margins; sm, submucosal; sm1, superficial invasion in the submucosa (less than 200 micrometres below the muscularis mucosae

Study details	Key efficacy findings	Key safety findings	Comments
Oda I (2006)[3] **Non-randomised comparative study** Japan Recruitment period: 2001 Study population: EGC n = **655 (714 lesions: 303 ESD vs 411 EMR)** **Mean age**: 67 years (ESD), 68 years (EMR) Sex: 78% (ESD), 77% (EMR) **Location**: ESD – upper third (48), middle third (122), lower third (133); EMR – upper third (75), middle third (126), lower third (206), unknown (8) **Depth**: not reported **Elevated lesions**: 34% (103) ESD and 53% (217) EMR **Mean size**: ESD – > 20 mm without ulceration (44), ≤ 30 mm with ulceration (58); EMR – > 20 mm without ulceration (44), ≤ 30 mm with ulceration (58) Inclusion criteria: histologically confirmed differentiated adenocarcinoma, endoscopically shown (including EUS) to be limited to m or sm1 (≤ 500 μm depth into the submucosa), no ulcer or 30 mm or less with an ulcer Exclusion criteria: other cancers, previous treatment of EGC with endoscopic procedure, and residual or recurrent EGC diagnosed in gastric tube reconstruction after oesophagectomy or in a remnant stomach after gastrectomy	Number of patients analysed: **655 (714 lesions: 303 ESD vs 411 EMR)** *Completeness of resection* Curative resection: tumour-free margins, non-evaluable: difficult histological assessment |	**ESD**	**EMR**
---	---	---
Curative resection*	73.6% (223/303)	61.1% (251/411)
Non-curative resection*	18.2% (55/303)	20.4% (84/411)
Non-evaluable resection	8.3% (25/303)	18.5% (76/411)	 Of the 92.7% (281/303) and 56.0% (230/411), respectively, resected en-bloc: 	**Curative resection***	71.9% (218/303)	41.8% (172/411)
Non-curative resection*	17.2% (52/303)	10.0% (41/411)
Non-evaluable resection*	3.6% (11/303)	4.1% (17/411) | Of the 7.3% (22/303) and 44.0% (181/411), respectively, resected piecemeal: | **Curative resection***	1.7% (5/303)	19.2% (79/411)		*Complications* Blood transfusion because of bleeding was required in 1 patient treated with EMR. Perforation was significantly higher in those treated with ESD than EMR (3.6% (11/303) vs 1.2% (5/411); p < 0.05). All were managed endoscopically (no other details provided about the timing of perforation or the type of endoscopic procedure used to manage the perforation). There were no deaths related to the procedure.	**Follow-up issues**: • Arrangements for follow-up were not described. **Study design issues**: • This was a retrospective study of patients treated at 11 institutions with the intention of determining the results of EMR and ESD nationwide. **Study population issues**: • Patients treated with ESD had significantly less elevated lesions, **Other issues**: • 80.0% (568/714) lesions were diagnosed using the general indications of endoscopic resection before treatment and 20.4% (146/714) were diagnosed with expanded indications.

Abbreviations used: APC, argon plasma coagulation; CT, computed topography; EGC, early gastric cancer; EGD, esophagogastroduodenoscopy; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; EUS, endoscopic ultrasound; GIST, gastro-intestinal stromal tumour; IMC, intramucosal cancer; JGCA, Japanese Gastric Cancer Association; M, mucosal; R0, en-bloc resection with tumour-free margins; R1, en-bloc resection without tumour-free margins; sm, submucosal; sm1, superficial invasion in the submucosa (less than 200 micrometres below the muscularis mucosae				
Study details	**Key efficacy findings**		**Key safety findings**	**Comments**
Technique: EMR (including strip biopsy [with 2-channel endoscope], aspiration mucosectomy [with transparent cap] and using a ligating device) and ESD Maximum follow-up: **5 years** Conflict of interest/source of funding: the study was supported by the JGCA	**Non curative resection**	1.0% (3/303)	10.5% (43/411)		
	Non-evaluable resection*	4.6% (14/303)	14.4% (59/411)		
	*p < 0.01 ***Local recurrence*** (Patients followed up for less than 6 months excluded.) Residual (within 6 months) or recurrent (after 6 months) were found in 2.0% (6/303) treated by ESD and 6.6% (27/411) treated by EMR in a median follow-up period of 3.2 years (from 0.5 to 5 years; significance not reported). None of these patients had curative resections. One tumour which had an additional EMR re-recurred. (Subsequent treatment of residual or recurrent treatments not described.) ***Survival*** There were no deaths related to gastric cancer but there were 6 patients who died of other causes. 3-year residual-free/recurrence-free, residual-free/recurrence-free survival and overall survival were 94.4%, 93.7% and 99.2%, respectively. The residual-free/recurrence-free rate and the residual-free/recurrence-free survival rates were higher in the ESD group than the EMR groups (ESD 97.6% vs EMR 92.5%, p = 0.01 and				

Abbreviations used: APC, argon plasma coagulation; CT, computed topography; EGC, early gastric cancer; EGD, esophagogastroduodenoscopy; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; EUS, endoscopic ultrasound; GIST, gastro-intestinal stromal tumour; IMC, intramucosal cancer; JGCA, Japanese Gastric Cancer Association; M, mucosal; R0, en-bloc resection with tumour-free margins; R1, en-bloc resection without tumour-free margins; sm, submucosal; sm1, superficial invasion in the submucosa (less than 200 micrometres below the muscularis mucosae

Study details	Key efficacy findings	Key safety findings	Comments
	96.1% vs 92.2%, respectively; p = 0.04). There was no difference in overall survival.		

Abbreviations used: APC, argon plasma coagulation; CT, computed topography; EGC, early gastric cancer; EGD, esophagogastroduodenoscopy; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; EUS, endoscopic ultrasound; GIST, gastro-intestinal stromal tumour; IMC, intramucosal cancer; JGCA, Japanese Gastric Cancer Association; M, mucosal; R0, en-bloc resection with tumour-free margins; R1, en-bloc resection without tumour-free margins; sm, submucosal; sm1, superficial invasion in the submucosa (less than 200 micrometres below the muscularis mucosae

Study details	Key efficacy findings			Key safety findings			Comments
Min BH (2008)[4]	**Number of patients analysed: 346 (243 ESD vs 103 EMR)**			*Complications*			**Follow-up issues**:
Non-randomised comparative study					**ESD**	**EMR**	• EGD with biopsy at 1 month and then every 3 months for a year, then every 6 months until the 4th year when this was done annually.
Korea	*Completeness of resection*			Postoperative bleeding	5.3% (13/243)	3.9% (4/103)	
Recruitment period:		**ESD**	**EMR**	Total perforations	4.5% (11/243)	1.9% (2/103)	
2003–2006	En-bloc resection*	95.9% (233/243)	77.7% (80/103)	'Frank' perforation	3	1	
Study population: EGC	By size (mm):			Microperforation	8	1	**Study design issues**:
n = 346 (243 ESD vs 103 EMR)	< 10	93.1 % (54/58)	86.8% (33/38)	(these were not significantly different)			• All patients were treated with EMR and ESD at this institution.
Mean age: 61.8 years (ESD), 61.3 years (EMR) **Sex**: 78.6% male (ESD), 73.8% (EMR) **Location**: ESD – antrum (157), angle (37), body (49), EMR – antrum (66), angle (12), body (24), fundus (1)	10–19* ≥ 20*	98.2% (112/114) 94.4% (67/71)	83.3% (40/48) 41.2% (7/17)	'Frank' perforations – when mesenteric fat or intraabdominal space was observed during the procedure 'Microperforations' – when free-air was found on a plain chest X-ray after the procedure but without visible gastric wall defect during the procedure			**Study population issues**: • 28 patients who did not meet the selection criteria were included because they had adenoma and refused to undergo, or were contraindicated, for surgery.
Depth: not reported **Macroscopic appearance**: ESD – elevated (148), flat or depressed (95), EMR –elevated (75), flat or depressed (28)	R0 resection	93.0% (226/243)	89.3% (92/103)				
Size: ESD – < 10 mm (58), 10–19 mm (114), 20–29 mm (45), ≥ 30 mm (26), EMR – < 10 mm (38), 10–19 mm (48), 20–29 mm (12), ≥ 30 mm (5)	By size (mm): < 10 10-19 ≥ 20***	100 % (58/58) 92.1% (105/114) 88.7% (63/71)	97.4% (37/38) 93.8% (45/48) 58.8% (10/17)	One patient with bleeding in the EMR group required emergency surgery. All other patients were successfully managed with metallic clips or coagulation of the bleeding vessels.			• Those with ESD had significantly more patients with flat or depressed and ≥ 20 mm lesions.
Patient selection criteria: intramucosal lesion (on endoscopy), well or moderately differentiated (on biopsy), no ulcer or ulcer scar (on endoscopy) or lymph node involvement or distant metastases (on CT scan)	R0 and en-bloc**	88.9% (216/243)	75.7% (78/103)	The patient with a frank perforation treated with EMR required emergency surgery, but all the others were successfully managed non-surgically with a combination of endoscopic clipping, fasting, nasogastric tube drainage and broad-spectrum antibiotics.			**Other issues**: • Patients had
Technique: EMR (with circumferential pre-cutting) and ESD Maximum follow-up: **37 months (ESD), 44**	By size (mm): < 10 10-19 ≥ 20*	93.1 % (54/58) 90.4% (103/114) 83.1% (59/71)	86.8% (33/38) 81.3% (39/48) 35.3% (6/17)				

Abbreviations used: APC, argon plasma coagulation; CT, computed topography; EGC, early gastric cancer; EGD, esophagogastroduodenoscopy; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; EUS, endoscopic ultrasound; GIST, gastro-intestinal stromal tumour; IMC, intramucosal cancer; JGCA, Japanese Gastric Cancer Association; M, mucosal; R0, en-bloc resection with tumour-free margins; R1, en-bloc resection without tumour-free margins; sm, submucosal; sm1, superficial invasion in the submucosa (less than 200 micrometres below the muscularis mucosae

Study details	Key efficacy findings	Key safety findings	Comments
months (EMR) Conflict of interest/source of funding: none	*p < 0.001, ** p = 0.002, ***p = 0.008 These differences were not significantly different when results were further subdivided by macroscopic appearance. 1 patient in the EMR group and 4 in the ESD group underwent surgeries after the procedure because of tumour-free lateral resection margins < 2 mm. ***Local recurrence*** Only those with R0 resection with intramucosal differentiated cancer were included. There were no recurrences (defined as cancer detected at resection site after 2 negative follow-ups) in either the 80 patients followed up in the EMR group or the 191 followed up in the ESD group (at a median of 29 months and 17 months follow-up, respectively). Residual tumours (found in the 2 scheduled follow-up sessions within the 12 months after the procedure) were found in 2.8% (2/72) in the EMR group and 0.56% (1/180) in the ESD group. - The first 2 were in patients who were treated piecemeal and were detected in their first follow-up after EMR; one was treated with surgery and the other with ESD. Both were recurrence-free at 25		preoperative endoscopy and biopsy.

Abbreviations used: APC, argon plasma coagulation; CT, computed topography; EGC, early gastric cancer; EGD, esophagogastroduodenoscopy; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; EUS, endoscopic ultrasound; GIST, gastro-intestinal stromal tumour; IMC, intramucosal cancer; JGCA, Japanese Gastric Cancer Association; M, mucosal; R0, en-bloc resection with tumour-free margins; R1, en-bloc resection without tumour-free margins; sm, submucosal; sm1, superficial invasion in the submucosa (less than 200 micrometres below the muscularis mucosae

Study details	Key efficacy findings	Key safety findings	Comments
	and 30 months. - The latter which was successfully treated en-bloc with ESD was also detected in the first follow-up, 1 month after the procedure. This patient had surgery for the residual tumour and was recurrence-free during the 35 months of follow-up.		

Abbreviations used: APC, argon plasma coagulation; CT, computed topography; EGC, early gastric cancer; EGD, esophagogastroduodenoscopy; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; EUS, endoscopic ultrasound; GIST, gastro-intestinal stromal tumour; IMC, intramucosal cancer; JGCA, Japanese Gastric Cancer Association; M, mucosal; R0, en-bloc resection with tumour-free margins; R1, en-bloc resection without tumour-free margins; sm, submucosal; sm1, superficial invasion in the submucosa (less than 200 micrometres below the muscularis mucosae

Study details	Key efficacy findings	Key safety findings	Comments
Nakamato S (2009)[5] **Non-randomised comparative study** Japan Recruitment period: 1999–2003 (EMR), 2003–2007 (ESD) Study population: EGC n = **177 (106 ESD vs 71 EMR) (202 lesions: 122 ESD vs 80 EMR)** **Mean age**: 68.4 years (ESD), 66 years (EMR) **Sex**: 77% male (ESD), 72% male (EMR) **Location**: ESD – upper third (10), middle third (44), lower third (68), EMR – upper third (9), middle third (32), lower third (39) **Macroscopic type**: ESD – elevated (73), flat or depressed (49), EMR – elevated (55), flat or depressed (25) **Depth**: not reported **Histology**: ESD – well-differentiated (113), moderately-differentiated (9), EMR, well-differentiated (76), moderately differentiated (4) **Mean size**: ESD – ≤ 5 mm (9), 6–10 mm (42), 11–15 mm (38), 16–20 mm (33), EMR – ≤ 5 mm (7), 6–10 mm (23), 11–15 mm (28), 16–20 mm (22) Patient selection criteria: patients met the JGCA guidelines for EMR Technique: EMR with 2-channel endoscope	Number of patients analysed: **177 (106 ESD vs 71 EMR) (202 lesions: 122 ESD vs 80 EMR)** ***Completeness of resection*** Complete resection: en-bloc resection with tumour-free margins |	ESD	EMR
---	---	---
En-bloc resection	94.3% (115/122)	53.8% (43/80)
By size (mm): ≤ 5 6–10 11–15 16–20	100% (9/9) 97.6% (41/42) 97.4% (37/38) 84.8% (28/33)	100% (7/7) 60.9% (14/23) 60.7% (17/28) 22.7% (5/22)
Complete resection	92.6% (113/122)	37.5% (30/80)
By size (mm): ≤ 5 6–10 11–15 16–20	88.9% (8/9) 95.2% (40/42) 97.4% (37/38) 84.8% (28/33)	71.4% (5/7) 47.8% (11/23) 42.9% (12/28) 9.1% (2/22) | (all were p < 0.001 except for both en-bloc and complete resections for	***Complications*** |	ESD	EMR
---	---	---
Bleeding requiring transfusion	1.6% (2/122)	0% (0/80)
Perforation	2.5% (3/122)	0% (0/0) | (these were not significantly different) 1 patient with perforation required abdominal surgery and the others recovered with conservative management (endoscopic clipping, nasogastric aspiration, parenteral nutrition support and antibiotic therapy). Bleeding was controlled endoscopically with electrocoagulation or haemoclipping.	**Follow-up issues**: • Endoscopy at 6 and 12 months and then annually (complete resection); 1, 3, 6, 12 months (incomplete resection). **Study design issues**: • Retrospective study of all patients who filled the JGCA criteria. **Study population issues**: • No significant difference in age, sex, tumour size, location, macroscopic type or histology. **Other issues**: • Pre-diagnostic assessment was not described.

Abbreviations used: APC, argon plasma coagulation; CT, computed topography; EGC, early gastric cancer; EGD, esophagogastroduodenoscopy; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; EUS, endoscopic ultrasound; GIST, gastro-intestinal stromal tumour; IMC, intramucosal cancer; JGCA, Japanese Gastric Cancer Association; M, mucosal; R0, en-bloc resection with tumour-free margins; R1, en-bloc resection without tumour-free margins; sm, submucosal; sm1, superficial invasion in the submucosa (less than 200 micrometres below the muscularis mucosae			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
and ESD, both with intravenous sedation Maximum follow-up: **62 months (ESD), 89 months (EMR)** Conflict of interest/source of funding: not reported	lesions ≤ 5 mm) ***Local recurrence and survival*** Patients were followed up for a median of 54 months (EMR) and 34 months (ESD). The overall recurrence-free rate was significantly lower in the EMR group than the ESD group (82.5% [66/80] vs 100% [122/122]; p < 0.001). Of the 14 with recurrences in the EMR group, 3 required surgery and 11 were re-treated endoscopically. *Subgroup analysis:* For lesions larger than 10 mm, the 5-year recurrence-free rate was significantly lower in the EMR group compared with the ESD group (74% vs 100%; p < 0.001; absolute figures not reported) For lesions ≤ 10 mm, the 5-year recurrence-free rate was not significantly different (96.7% vs 100%; p = 0.19; absolute figures not reported). There were no recurrences in patients with lesions ≤ 5 mm.		

Abbreviations used: APC, argon plasma coagulation; CT, computed topography; EGC, early gastric cancer; EGD, esophagogastroduodenoscopy; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; EUS, endoscopic ultrasound; GIST, gastro-intestinal stromal tumour; IMC, intramucosal cancer; JGCA, Japanese Gastric Cancer Association; M, mucosal; R0, en-bloc resection with tumour-free margins; R1, en-bloc resection without tumour-free margins; sm, submucosal; sm1, superficial invasion in the submucosa (less than 200 micrometres below the muscularis mucosae

Study details	Key efficacy findings	Key safety findings	Comments
Probst A (2009)[6] **Case series** Germany Recruitment period: 2003–2007 Study population: premalignant and early malignant gastrointestinal lesions n = **59 lesions** **Type**: EGC (34), flat adenoma (15), submucosal tumour (10: 3 pancreatic heterotopias, 2 GIST, 2 neuroendocrine tumours, 1 leiomyoma, 1 lipoma, 1 hyperplastic polyp) Of the 51 lesions treated: **Location**: upper stomach (2 EGC, 1 adenoma), middle stomach (7 EGC, 1 adenoma), lower stomach (21 EGC, 1 adenoma) **Histopathology**: protruding (2), flat (27), excavated (1) **Ulcers**: 6 (type II) and 1 (type III) **Mean size of resected specimen**: 37.2 mm (EGC), 36.1 mm (flat adenoma), 17.9 mm (submucosal) Of all 78 patients treated for entire gastrointestinal tract: **Mean age**: 67.1 years **Sex**: 57.7% male Patient selection criteria: extended JGCA guidelines Technique: ESD with sedation (3 cases used	Number of patients analysed: **51 lesions (30 EGC, 14 flat adenoma, 7 submucosal)** (See 'comments' section for reasons why not all 59 patients included in analysis) ***Completeness of resection*** <table><tr><td></td><td>**En-bloc resection**</td><td>**R0 resection**</td></tr><tr><td>**All lesions**</td><td>86.3% (44/51)</td><td>72.5% (37/51)</td></tr><tr><td>**Epithelial gastric lesions**</td><td>84.1% (37/44)</td><td>70.5% (31/44)</td></tr><tr><td>**Submucosal tumours**</td><td>100% (7/7)</td><td>85.7% (6/7)</td></tr></table> Of the 4 patients with residual tumours in the deep margin (R1 lesions), 3 had gastrectomy and the 4th refused. Neither of the 2 with R1 resection in the lateral margins had residual macroscopic lesions and so did not have surgery. ***Local recurrence (mean 15.5 months)*** One of the patients treated with gastrectomy was diagnosed with diffuse hepatic metastases 3 months after gastrectomy. The others were disease-free at the time of writing. 2 patients (1 EGC, 1 adenoma) had	***Complications*** <table><tr><td>**Event**</td><td>**No. of patients**</td></tr><tr><td>**Perforation***</td><td>2</td></tr><tr><td>**Minor bleeding**</td><td>8</td></tr><tr><td>**Symptomatic pyloric stenosis****</td><td>3</td></tr></table> (denominator not clear in the study so rates not calculable) *These were detected during the procedure and were treated with surgery (both were in submucosal tumours with diameter of 3 cm) **Time of occurrence not reported; all were in the distal stomach; successful balloon dilation was performed in 2, but 1 patient was not referred for endoscopic treatment of the pyloric stenosis because the patient was referred for surgery due to cancer recurrence in the ESD scar There were no deaths.	**Follow-up issues**: • For R0 resection, endoscopy every 3 months in 1st year and every 6 months afterwards. After R1 resections, endoscopy also after 4 to 6 weeks. **Study design issues**: • Patients were referred to this centre. • Study reports on 78 patients treated in entire gastrointestinal tract. **Other issues**: • This study has been included in this table because the patients (from Germany) may be more generalisable to the UK population. • Chromoendoscopy with indigo carcmin, autofluorescence endoscopy, narrow-band imaging or a combination of these techniques was added to conventional white-

Abbreviations used: APC, argon plasma coagulation; CT, computed topography; EGC, early gastric cancer; EGD, esophagogastroduodenoscopy; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; EUS, endoscopic ultrasound; GIST, gastro-intestinal stromal tumour; IMC, intramucosal cancer; JGCA, Japanese Gastric Cancer Association; M, mucosal; R0, en-bloc resection with tumour-free margins; R1, en-bloc resection without tumour-free margins; sm, submucosal; sm1, superficial invasion in the submucosa (less than 200 micrometres below the muscularis mucosae			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
general anaesthetic) Maximum follow-up: **43 months** Conflict of interest/source of funding: none	metachronous gastric lesions (recurrence at other sites) 6 and 16 months after the initial ESD (both were treated successfully with ESD; it was not clear if these patients were originally treated with en-bloc or piecemeal resection). Local recurrence at the site of initial ESD occurred in 3 patients with EGC and 2 patients with gastric adenoma at 3, 4, 5, 4, and 8 months respectively, after piecemeal ESD. All patients with EGC were treated with gastrectomy and all patients with adenomas were treated endoscopically. There were no recurrences in those with an R0 resection.		light endoscopy. • The study does not clearly state why all 8 lesions were not treated with ESD. 4 cases could not be performed because the lesion would not lift after submucosal injection (3 were then treated surgically and 1 endoscopically). The reasons for this were not clear but 2 patients appeared to have submucosal invasion. It is not clear what the reasons were for the exclusion of 4 more patients for the analysis. It may include the 2 patients with perforation for whom the procedure was terminated.

Abbreviations used: APC, argon plasma coagulation; CT, computed topography; EGC, early gastric cancer; EGD, esophagogastroduodenoscopy; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; EUS, endoscopic ultrasound; GIST, gastro-intestinal stromal tumour; IMC, intramucosal cancer; JGCA, Japanese Gastric Cancer Association; M, mucosal; R0, en-bloc resection with tumour-free margins; R1, en-bloc resection without tumour-free margins; sm, submucosal; sm1, superficial invasion in the submucosa (less than 200 micrometres below the muscularis mucosae

Study details	Key efficacy findings	Key safety findings	Comments
Coda S (2009)[7] **Case series** Japan Recruitment period: 2000–2005 Study population: EGC n = **1819 (2011 lesions)** **Median age**: 68 years **Sex**: 79.7% male **Location**: upper third (326), middle third (887), lower third (798) Of the 156 with cardiac (n = 41) or pyloric (n = 115) resections (where stenosis occur): **Depth**: mucosal (128), submucosal (28) **Mean size**: ≤ 5 cm (148), > 5 cm (8) **Macroscopic type**: elevated (46), depressed (89), elevated and depressed (21) Patient selection criteria: not reported Technique: ESD Follow-up: **36 months** Conflict of interest/source of funding: none	Not the purpose of the study	Number of patients analysed: **1819 (2011 lesions)** *Stenosis* Gastric stenosis was diagnosed endoscopically when a standard 10 mm diameter endoscope could not pass through the stenosis. 0.7% (15/2011) of lesions had stenosis (in 15 of 1819 patients) which were diagnosed at a median of 22 days after ESD in those with cardiac resection (n = 41) and 27 days after ESD in those with pyloric resection (n = 115). 17.0% (7/41) of cardiac resections (in upper third) and 7.0% (8/115) of the pyloric resections (lower third) resulted in stenosis. All required endoscopic balloon dilation treatment and symptoms completely resolved in every patient in a median of 5 dilations for the cardiac resections and 9 for the pyloric resections. *Perforation* Of the 156 patients treated with ESD in the cardia or pylorus, 10.0% (4/41) and 1.7% (2/115), respectively had perforation. (overall perforation rate in the 1819 patients not reported).	**Follow-up issues**: • Follow-up endoscopy was performed after 2–3 months to check the healing process (but this was earlier (not reported) for those who had cardiac or pyloric resection) and then every 6 months or annually. **Study design issues**: • The purpose of this study was to look at the risk factors for post-ESD stenosis. • Resection was cardiac when a mucosal defect was located in the squamocolumnar junction; it was pyloric when the mucosal defect was located < 1 cm from the pylorus ring **Other issues**: • A lesion covering > three-quarters of the stomach or a length of > 5 cm were significant risk factors for post-ESD stenosis.

Abbreviations used: APC, argon plasma coagulation; CT, computed topography; EGC, early gastric cancer; EGD, esophagogastroduodenoscopy; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; EUS, endoscopic ultrasound; GIST, gastro-intestinal stromal tumour; IMC, intramucosal cancer; JGCA, Japanese Gastric Cancer Association; M, mucosal; R0, en-bloc resection with tumour-free margins; R1, en-bloc resection without tumour-free margins; sm, submucosal; sm1, superficial invasion in the submucosa (less than 200 micrometres below the muscularis mucosae			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Kobayashi N (2007)[8] **Case report** Japan n = **1** 61-year old male with EGC and history of colectomy from Crohn's disease Technique: ESD Follow-up: **14 months** Conflict of interest/source of funding: supported in part by Grant-in-Aid for Cancer Research from the Ministry of Health, Labour and Welfare	A second ESD procedure was required because of metachronous cancer. Gastric perforation occurred during the procedure but was closed with endoscopic clips and antibiotics were administered (with fasting). 12 hours after the procedure, laboratory data showed significant increase in aspartate and alanine aminotransferase, lactate dehydrogenase, creatine phosphokinase, C-reactive protein and white blood cell count. Abdominal CT scan showed severe **pneumoperitoneum** compressing on the inferior vena cava so abdominal decompression was performed with a 14-gauge puncture needle. All lab tests were normal 4 days later and there were no further events over the following 14 months.		
Jang CS (2007)[9] **Case report** Korea n = **1** 66-year old female with EGC type IIc (with mucosal depression), 15 mm in diameter located in the cardia Technique: ESD Follow-up: **6 weeks** Conflict of interest/source of funding: not reported	Dyspnea and abdominal pain with distension occurred immediately after ESD. Chest radiography showed **pneumoperitoneum and left pneumothorax**. The patient was treated with pigtail catheter insertion into the left pleural space with oxygen inhalation followed by administration of proton-pump inhibitor, antibiotics and fasting. Both were improved 5 days later and ESD ulcer without bleeding or further complications was shown on follow-up endoscopy. The lateral margin was clear but the tumour had invaded the submucosa. The patient chose not to have further surgery so was discharged 7 days later. No evidence of malignancy 6 weeks later.		

Abbreviations used: APC, argon plasma coagulation; CT, computed topography; EGC, early gastric cancer; EGD, esophagogastroduodenoscopy; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; EUS, endoscopic ultrasound; GIST, gastro-intestinal stromal tumour; IMC, intramucosal cancer; JGCA, Japanese Gastric Cancer Association; M, mucosal; R0, en-bloc resection with tumour-free margins; R1, en-bloc resection without tumour-free margins; sm, submucosal; sm1, superficial invasion in the submucosa (less than 200 micrometres below the muscularis mucosae			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Tanaka K (2009)[10] **Case report** Japan n = **1** 78-year old male with history of diabetes mellitus, hypertension, hyperlipidemia, and myocardial infarction with papillary adenocarcinoma in three-fourths of pylorus extending into the duodenum Technique: ESD Follow-up: **6 months** Conflict of interest/source of funding: none	1 week after a complete resection with ESD with no complications, endoscopy revealed ulcer extending three fourths around the pylorus. 2 months after ESD, the patient developed anorexia and **pyloric stenosis** was documented so balloon dilatation was performed. 6 months later, the patient was admitted to hospital because of staggering gait, profound disorientation, indifference and inattentiveness. Laboratory tests showed the patient had anemia, low serum thiamine levels but normal serum vitamin B_{12} and folate levels. The patient was diagnosed with **Wernicke's encephalopathy** which was treated successfully with thiamine.		
Tajika M (2009)[11] **Case report** Japan n = **1** 64-year old male with well-differentiated adenocarcinoma (preoperative EGC) and history of anemia, duodenal ulcer, hypertension, depression. Technique: ESD Follow-up: **2 weeks** Conflict of interest/source of funding: not reported	After the ESD was performed en-bloc, there were no immediate complications (perforations or major bleeding). The second day after the procedure the patient reported nausea and lethargy. The patient had low serum sodium levels and fulfilled criteria of syndrome of inappropriate secretion of antidiuretic hormone (SIADH; diabetes insipidus). The patient recovered after fluid restriction, infusion of normal saline and administration of diuretics in 2 weeks.		

Efficacy

Completeness of resection

A non-randomised comparative study of 900 malignant lesions (patient numbers not reported) comparing 572 lesions treated with ESD with 328 lesions with EMR showed a significantly larger complete resection and curative resection (with tumour-free margins) in patients treated by ESD (95% [544/572] vs 64% [210/328] and 83% [473/572] vs 60% [195/328], respectively; p < 0.05 for both)[1].

A non-randomised comparative study of 896 patients (1020 malignant lesions) reported a significantly greater complete en-bloc and histological resection rate in lesions without ulceration treated with ESD than EMR (93% [157/169] vs 43% [343/790] and 93% [157/169] vs 25% [194/790], respectively; p < 0.01). In ulcerated lesions, en-bloc resection rate was not significantly different in the two groups but the histological resection rate was significantly greater in those treated by ESD (19% [5/26] vs 3% [1/35]; p < 0.056)[2].

 A non-randomised comparative study of 655 patients (714 malignant lesions) reported that en-bloc resection and curative resection was significantly greater in patients treated with ESD (93% [281/303] vs 56% [230/411] and 74% [223/303] vs 61% [251/411], respectively; p < 0.01 for both). The same study reported that 8% (25/303) and 19% (76/411) of patients treated with ESD and EMR, respectively were not evaluable because of a difficult histological assessment[3].

A non-randomised comparative study of 346 patients (number of lesions not reported) reported a significantly greater en-bloc resection and R0 plus en-bloc resection in patients treated with ESD than patients treated with EMR (96% [233/243] vs 78% [80/103] and 89% [216/243] vs 76% [78/103], respectively]; p < 0.001 and p = 0.002, respectively). When divided into subgroups by size, the differences remained significant for lesions greater than or equal to 20 mm (p < 0.001 for both outcomes)[4].

A non-randomised comparative study of 177 patients (202 lesions) reported significantly greater en-bloc resection and en-bloc resection with tumour-free margin rates in patients treated with ESD than patients treated with EMR (94% [115/122] vs 54% [43/80] and 93% [113/122] vs 38% [30/80], respectively; p < 0.001). When subdivided by size, lesions less than or equal to 5 mm were not significant different between ESD and EMR[5].

A case series of 59 pre-malignant or malignant lesions (patient numbers not reported) reported en-bloc resection in 86% (44/51) and R0 resection in 73% (37/51)[6].

Survival and local recurrence

The non-randomised comparative study of 900 malignant lesions reported that there were no recurrences among those treated with ESD and 4% (13/328)

lesions recurred in those treated with EMR (time of occurrences and mode of treatment not reported; p < 0.05)[1].

The non-randomised comparative study of 896 patients (1020 malignant lesions) reported no recurrences in patients treated with ESD at a mean follow-up of 19.4 months. In patients treated by EMR, there were recurrences in 3% (10/347) with en-bloc resection and 4% (21/478) with piecemeal resection over a mean follow-up of 83.2 months. All local recurrences were treated with additional endoscopic treatment or surgery (time of detection not reported)[2].

The non-randomised comparative study of 655 patients (714 malignant lesions) reported that among patients followed up longer than 6 months, there was recurrence in 2% (6/303) of lesions treated with ESD and 7% (27/411) of lesions treated with EMR in a median follow-up of 3.2 years (significance and subsequent treatment not described). None of these were patients with a curative resection[3].

The non-randomised comparative study of 346 patients with malignant lesions reported no recurrences among patients with R0 resection and intramucosal differentiated cancer. There were no recurrences in the 191 treated by ESD or the 80 treated with EMR at a median of 17 and 29 months follow-up, respectively[4].

The non-randomised comparative study of 177 patients (202 malignant lesions) reported that the overall recurrence-free rate was significantly higher in the ESD group than the EMR group over a median follow-up of 34 and 54 months, respectively (100% [122/122] vs 83% [14/80]; p < 0.001). When a subgroup analysis was performed, the 5-year recurrence-free rate was significantly higher in the ESD group lesions larger than 10 mm but there was no statistically significant difference for lesions less than or equal to 10 mm[5].

The case series of 59 pre-malignant or malignant lesions reported that one patient treated with gastrectomy for residual margins after ESD was diagnosed with diffuse hepatic metastases 3 months after the procedure[6].

In the same study, local recurrence at the treated site occurred in 5 patients treated with piecemeal ESD at 3, 4, 5, 4, and 8 months follow-up. Three patients with early gastric cancer were then treated with gastrectomy and two patients with adenomas were treated endoscopically.

The same study reported recurrence of gastric lesions at other sites: one patient with early gastric carcinoma and one patient with adenoma 6 and 16 months, respectively, after the initial ESD (both were treated successfully with ESD; it was not clear if these patients were originally treated with en-bloc or piecemeal resection).

Safety

Perforation

The non-randomised study of 900 malignant lesions reported perforation in 4% (20/572) and 2% (5/328) of patients treated with ESD and EMR, respectively (not significant; treatment of perforations not described)[1].

The non-randomised study of 896 patients (1020 malignant lesions) reported different rates of perforation in the text and the table. In the table, perforation occurred in those without ulceration significantly more with EMR than ESD (11% [19/169] vs 0.5% [4/790]; p < 0.01). The text reported that there were a total of 13 perforations (7%) in the ESD group and 0.5% (4/825) in the EMR group. It stated that 31% (4/13) in the ESD group required surgery and all others were successfully treated conservatively[2].

The non-randomised study of 655 patients (714 malignant lesions) reported that perforation was significantly higher in those treated with ESD than EMR (4% [11/303] vs 1% [5/411] lesions; p < 0.05). All were managed endoscopically (no other details provided about the timing of perforation or the type of endoscopic procedure used to manage the perforation)[3].

The non-randomised comparative study of 346 patients with malignant lesions reported 5% (11/243) and 2% (2/103) of perforations in patients treated with ESD and EMR, respectively (not significant). Three of those treated with ESD and one treated by EMR were detected during the procedure and the others were discovered after the procedure (time of detection not reported). The patient with the perforation in the EMR group detected during the procedure required emergency surgery but all other patients were managed non-surgically with a combination of endoscopic clipping, fasting, nasogastric tube drainage and antibiotics[4].

The case series of 59 pre-malignant or malignant lesions reported 2 perforations detected during the procedure which were treated with surgery (both were in submucosal tumours with diameter of 3 cm)[6].

A case report of a patient with gastric perforation which was closed with endoscopic clips during ESD was shown later to have pneumoperitoneum compressing on the inferior vena cava. The patient was treated successfully with abdominal decompression in the next 4 days and there were no further events over the following 14 months[8].

Another case report of a patient presenting with dyspnea and abdominal pain with distension immediately after ESD was shown to have pneumoperitoneum and left pneumothorax. The patient had improved 5 days later[9].

Stricture

A case series of 1819 patients (2011 malignant lesions) reported stenosis after ESD in 0.7% (15/2011) of lesions: 17% (7/41) patients with cardiac resections and 7% (8/115) with pyloric resections (time of occurrence not reported) [7]. All had successfully resolved after endoscopic balloon dilation treatment. The case series of 59 lesions reported symptomatic pyloric stenosis in 3 patients (time of occurrence not reported). This was successfully treated with balloon dilation in 2; the other patient was referred for surgery because of cancer recurrence[6].

A case report of a patient with adenocarcinoma extending to three-fourths of the pylorus and into the duodenum developed Wernicke's encephalopathy as a complication of pyloric stenosis 6 months after treatment with ESD. This was successfully treated with thiamine[10].

Bleeding requiring transfusion or surgery

In the non-randomised study of 896 patients (1020 malignant lesions), blood transfusions were required in 1 with ulceration in the ESD group and 2 without ulceration in the EMR group[2].

The non-randomised study of 655 patients reported that blood transfusion was required in 1 patient treated with EMR[3].

The non-randomised study of 346 patients reported that emergency surgery was required in one patient treated with EMR who had bleeding[4].

Other

A case report described a patient with adenocarcinoma who developed a symptomatic hyponatraemia because of diabetes insipidus (inappropriate secretion of antidiuretic hormone) 2 days after being treated with en-bloc ESD resection. This was successfully managed with fluid restriction, infusion of normal saline and administration of diuretics and the patient recovered in 2 weeks[11].

Validity and generalisability of the studies

- There are a large number of non-randomised studies comparing ESD with EMR.

- The maximum length of follow-up was 5 years[3].

- In order to manage the volume of search results, the literature search was restricted to papers published after 1999 to help focus on evidence using current versions of the technique. Also, only studies which reported on at least 100 patients were included in this overview, unless the study highlighted a

safety concern which was not already reported in this overview, or was reported at a significantly different rate than reported in this overview.

- The majority of studies are from Japan and Korea, where a substantial proportion of patients with gastric adenocarcinoma are diagnosed at an early stage, because of occupational-based screening schemes. Only one small European case series was identified and included in table 2, as it is likely that such evidence may be more directly applicable to UK patient populations and practice[6]. Another small case series of 19 European patients is included in appendix A (Dinis-Ribeiro M, 2009).

- A number of the studies refer to the Japanese Gastric Cancer Association (JGCA) guidelines but very few of the studies actually describe it. It appears that the original JGCA guidelines originally recommended dissection of lesions only when they were less than 20 mm (otherwise radical surgery should be performed). These guidelines were updated on the introduction of ESD to include lesions of any size for differentiated mucosal cancer without ulceration and less than 30 mm if ulceration was present. A large amount of the literature compares the outcomes from before and after the introduction of these extended indications (this is clearly pointed out in the comments section for each of these studies).

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B gives details of the recommendations made in each piece of guidance listed.

Interventional procedures

- Endoscopic submucosal dissection of lower gastrointestinal lesions. NICE interventional procedures guidance 335 (2010). Available from www.nice.org.uk/guidance/IPG335
- Laparo-endogastric surgery. NICE interventional procedures guidance 25 (2003). Available from www.nice.org.uk/guidance/IPG25

- Laparoscopic gastrectomy for cancer. NICE interventional procedures guidance 269 (2008). Available from www.nice.org.uk/guidance/IPG269

Clinical guidelines

- Dyspepsia: Managing dyspepsia in adults in primary care. NICE clinical guideline 17 (2004). Available from www.nice.org.uk/guidance/CG17

Specialist Advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and does not represent the view of the society.

Professor Hugh Barr, Dr Pradeep Bhandari, Brian Saunders, British Society of Gastroenterology.

- The Specialist Advisers considered the comparators to be surgical open resection with gastrectomy or laparoscopic local excision, endoscopic ablative therapies.

- There are less clinicians performing this procedure in the UK than overseas. The evidence reflects this as it is mostly from Japan by highly trained experts. This is important because the outcomes rely greatly on the expertise and skills of the endoscopist.

- Anecdotal adverse events include bleeding and perforation. Theoretically, perforation could lead to tumour seeding.

- The safety of the procedure is dependent on the skills and experience of the operator.

- Key efficacy outcomes include en-bloc and curative resection rates, recurrence rate, survival and mortality.

- The correct staging of early cancer and the failure to detect lymph node metastases are important.

- Training should involve animal models, use of a video library, training in lesion recognition and the decision-making process, followed by supervision by an expert. However, there are currently no experts in the UK. It should also be performed in a high-volume UK centre.

- One of the important considerations is whether or not this procedure could cure the cancer or if more radical procedures are required.

Patient Commentators' opinions

NICE's Patient and Public Involvement Programme sent questionnaires to 3 trusts for distribution to patients who had the procedure (or their carers), but did not receive any completed questionnaires.

Issues for consideration by IPAC

- None

References

1.   Hoteya S, Iizuka T, Kikuchi D et al. (2009) Benefits of endoscopic submucosal dissection according to size and location of gastric neoplasm, compared with conventional mucosal resection. Gastroenterology and Hepatology 24:1102–6

2.   Oka S, Tanaka S, Kaneko I et al. (2006) Advantage of endoscopic submucosal dissection compared with EMR for early gastric cancer. Gastrointestinal Endoscopy 64: 877–83

3.   Oda I, Saito D, Tada M et al. (2006) A multicentre retrospective study of endoscopic resection for early gastric cancer. Gastric Cancer 9: 262–70

4.   Min B-H, Lee JH, Kim JJ. (2008) Clinical outcomes of endoscopic submucosal dissection (ESD) for treating early gastric cancer: comparison with endoscopic mucosal resection after circumferential precutting (EMR-P). Digestive and Liver Disease 41: 201–9

5.   Nakamoto S, Sakai Y, Kasanuki J et al. (2009) Indications for the use of endoscopic mucosal resection for early gastric cancer in Japan: a comparative study with endoscopic submucosal dissection. Endoscopy 41: 746–50

6.   Probst A, Golger D, Arnholdt H et al. (2009) Endoscopic submucosal dissection of early cancers, flat adenomas, and submucosal tumors in the gastrointestinal tract. Clinical Gastroenterology and Hepatology 7: 149–55

7.   Coda S, Oda I, Gotoda T et al. (2009) Risk factors for cardiac and pyloric stenosis after endoscopic submucosal dissection, and efficacy of endoscopic balloon dilation treatment. Endoscopy 41: 421–6

8.   Kobayashi N, Ishikawa T, Fu K-I et al. (2007) Abnormal serum liver chemistry related to pneumoperitoneum after endoscopic submucosal dissection. Endoscopy 39: E327

9.   Jang CS, Park DK, Kwon KA et al. (2007) Pneumothorax as a complication of ESD. Endoscopy 39: E59

10.   Tanaka K, Aoki M, Hamada Y et al. (2009) Wernicke's encephalopathy caused by pyloric stenosis after endoscopic submucosal dissection. Gastrointestinal Endoscopy 69: 1170–1

11.   Tajika M, Nakamura T, Tsuboi J et al. (2009) Syndrome of inappropriate secretion of antidiuretic hormone after endoscopic submucosal dissection for early gastric cancer. Clinical Journal of Gastroenterology 2: 262–5.

Appendix A: Additional papers on endoscopic submucosal dissection of gastric lesions

The following table outlines the studies that are considered potentially relevant to the overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Abe Y, Inamori M, Iida H et al. (2009) Clinical characteristics of patients with gastric perforation following endoscopic submucosal resection for gastric cancer. Hepato-Gastroenterology 56: 921–4.	Case series n = 64 (67 lesions) Follow-up not reported	Perforations in 5.9% (4/67) lesions were treated successfully with conservative management. Perforations were associated with tumour size, location (upper region) and operation time.	Outcomes included in table 2.
Cao Y, Liao C, Tan A et al. (2009) Meta-analysis of endoscopic submucosal dissection versus endoscopic mucosal resection for tumors of the gastrointestinal tract. Endoscopy 41:751–7.	Meta-analysis of ESD for gastrointestinal lesions 15 non-randomised studies (9 early gastric cancer, 3 colorectal cancer, 3 oesophageal cancer)	En bloc resection was higher in those with ESD than EMR (odds ratio [OR]: 13.87 [10.12 – 18.99]; for gastric: 12.06 [8.40-17.30]) Local recurrence lower in ESD (5/1484) than EMR (118/2254) (OR 0.09, 95% confidence interval [CI]I 0.04–0.18, p = 0.000)	Outcomes were pooled but most included outcomes for colorectal and oesophageal lesions; difficult to determine outcomes for gastric lesions.
Chaves DM, Maluf Filho F, de Moura EG et al. (2010) Endoscopic submucosal dissection for the treatment of early esophageal and gastric cancer - initial experience of a western center. Clinics 65:377–82.	Case series n = 16 with gastric adenocarcinoma Mean follow-up = 9 months	All had free lateral and deep margins. No residual tumours or recurrences in follow-up. 2 cases of pneumomediastinum	Larger studies included in table 2. (this study is included despite having less than 100 patients because it is from a Western centre)
Chung IK, Lee JH, Lee SH et al. (2009) Therapeutic outcomes in 1000 cases of endoscopic submucosal dissection for early gastric neoplasms: Korean ESD Study Group multicenter study. Gastrointestinal Endoscopy 69: 1228–35.	Case series n = 952 (100 early gastric cancers) Follow-up = 12 months	Complete en-bloc resection: 87.7% (877/100) Recurrence in 10 1.2% (12/100) perforations: 11 managed with endoscopic clipping during the procedure and another required operation. Another operation was required in 1 patient with uncontrollable bleeding during ESD.	Comparative studies and studies with longer follow-up in table 2.

Dinis-Ribeiro M, Pimental-Nunes P, Afonso M et al. (2009) A European case series of endoscopic submucosal dissection for gastric superficial lesions. Gastrointestinal Endoscopy 69: 350–5.	Case series n = 19 (15 high-grade, 4 low-grade) Median follow-up = 10 months	89% (17/19) R0 resection 79% (15/19) en-bloc resection Major bleeding in 1 patient No perforations There was one recurrence during the follow-up period	Comparative studies and studies with longer follow-up in table 2.
Fujishiro M, Yahagi N, Kakushima N et al. (2006) Successful nonsurgical management of perforation complicating endoscopic submucosal dissection. Endoscopy 38: 1001–6.	Case series n = 528 gastrointestinal epithelial neoplasms Follow-up not reported	There were perforations in 27 lesions in 27 patients. 52% (14) were in the stomach. All but 3 during ESD (others unknown). All were successfully managed with endoscopic clips	This outcome is already reported in table 2 in larger studies.
Goto O, Fujishiro M, Kodashima S et al. (2009) Outcomes of endoscopic submucosal dissection for early gastric cancer with special reference to validation for curability criteria. Endoscopy 41: 118–22.	Case series n = 335 (385 early gastric cancer lesions) Median follow-up = 36 months	En-bloc with clear margins: 91.7% 2 local recurrences at 2 and 6 months At median 38 month follow-up, 5-year overall and disease-specific survival: 96.2% and 100% Perforations in 4%	Comparative studies in table 2.
Goto O, Fujishiro M, Kodashima S et al. (2009) Feasibility of electrocautery snaring as the final step of endoscopic submucosal dissection for stomach epithelial neoplasms. Digestive & Liver Disease 41: 26–30.	Comparative case series (of ESD with and without snare) n = 199 Follow-up = not reported	More patients without snaring had en bloc resection rate but this was only significant for tumours less than 2 cm There were proportionately more perforations in those with snaring but this was not significant	Larger studies included in table 2.
Goto O, Fujishiro M, Kodashima SA et al. (2010) A second-look endoscopy after endoscopic submucosal dissection for gastric epithelial neoplasm may be unnecessary: a retrospective analysis of postendoscopic submucosal dissection bleeding. Gastrointestinal Endoscopy 71:241–8.	Case series n = 454 lesions	Purpose of study to investigate post-ESD bleeding; 26 (5.7%) had post-ESD bleeding. Flat or depressed type was the only factor influencing bleeding. All occurred 14 days after ESD.	Comparative studies in table 2.
Hata K, Andoh A, Hayafuji K et al. (2009) Usefulness of bispectral monitoring of conscious sedation during	Case series n = 249 'cases'	Of a total of 366 patients treated for oesophageal, gastric and colonic lesions, 6 had brachycardia, 2	Larger studies included in table 2.

endoscopic mucosal dissection. World Journal of Gastroenterology 7: 595–8.		respiratory depression when bispectral monitoring was set at a lower level (these did not occur when set at a higher level).	
Hirasaki S, Kanzaki H, Matsubara M et al. (2007) Treatment of over 20 mm gastric cancer by endoscopic submucosal dissection using an insulation-tipped diathermic knife. World Journal of Gastroenterology 13 (29): 3981–4.	Non-randomised comparative study (between patients with lesions over 20 mm with patients with lesions less than 30 mm) n = 112 (40 > 20mm vs 72 < 20 mm) Follow-up not reported	Complete resection rate was not significantly different (85% > 20mm vs 89% < 20 mm) No significant differences in complications No recurrence reported	Larger studies with longer follow-up included in table 2.
Hirasaki S, Tanimizu M, Moriwaki T et al. (2004) Efficacy of clinical pathway for the management of mucosal gastric carcinoma treated with endoscopic submucosal dissection using an insulated-tip diathermic knife. Internal Medicine 43: 1120–5.	Non-randomised comparative study (before and after introduction of ESD at a centre) n = 23 ESD vs 20 control	(not clear of treatment prior to ESD) Significantly less length of stay in hospital in ESD group but not in operation time or bleeding rate	Larger studies with longer follow-up included in table 2.
Hotta K, Oyama T, Akamatsu T et al. (2010) A comparison of outcomes of endoscoic submucosal dissection (ESD) for early gastric neoplasms between high-volume and low-volume centres: multi-centre retrospective questionnaire study conducted by the Nagano ESD study group. Internal Medicine 49:253–9.	Case series n = 703 early gastric neoplasms (586 EGS, 117 gastric adenoma)	Complete en-bloc resection rate in those with post-operative diagnosis consistent with the JGCA standard indication (≤ 20 mm): 92.1% in high-volume centres, 91.1% in low-volume centres. For those with JGCA expanded indication (≤ 30 mm), these figures were 86.2% and 82.6%, respectively.	Comparative studies in table 2.
Ikehara H, Gotoda T, Ono H et al. (2007) Gastric perforation during endoscopic resection for gastric carcinoma and the risk of peritoneal dissemination. British Journal of Surgery 94: 992–5.	Case series n = 90 with perforations from ESD or EMR at an institution. Follow-up = median 53.6 months	83 patients had endoscopic clip and 7 required emergency surgery. Peritoneal fluid was tested and found cytologically negative for malignancy; no peritoneal dissemination was noted during follow-up.	Outcome reported in table 2.
Imaeda H, Hosoe N, Ida Y et al. (2009) Novel technique of endoscopic submucosal dissection using an external grasping forceps for	Case series n = 252 patients (265 lesions) Follow-up = not reported	95.8% (254/265) en bloc with tumour-free margins Major bleeding in 3.8% (10/265). 2 required blood transfusion.	Larger studies included in table 2.

		Perforation in one patient with adenoma 20mm. Patient recovered under observation	
superficial gastric neoplasia. Digestive Endoscopy 21:122–7.			
Imagawa A, Okada H, Kawahara Y et al. (2006) Endoscopic submucosal dissection for early gastric cancer: results and degrees of technical difficulty as well as success. Endoscopy 38: 987–90.	Case series n = 185 (196 lesions) Follow-up = 1 year	En bloc with clear resections: 84% Perforation rate: 6.1% (all managed endoscopically) No local recurrence in 119 lesions followed up at 1 year	Larger studies with longer follow-up included in table 2.
Isomoto H, Shikuwa S, Yamaguchi N et al. (2009) Endoscopic submucosal dissection for early gastric cancer: a large-scale feasibility study. Gut 58: 331–6.	Case series n = 551 (589 early gastric cancer lesions) Median follow-up = 30 months	En-bloc resection with clear margins: 94.7% (550/581) of lesions Patients with non-curative resection had more frequent local recurrence. Perforations in 4.5% (25) patients. 5-year overall and disease-specific survival 97.1% and 100%	Comparative studies and studies with longer follow-up in table 2.
Isomoto H, Ohnita K, Yamaguchi N et al. (2010) Clinical outcomes of endoscopic submucosal dissection in elderly patients with early gastric cancer. European Journal of Gastroenterology & Hepatology 22:311–7.	Case series n = 260 Median follow-up = 30 months	One-piece and complete resection rates significantly lower in elderly. Local recurrence: 0.6% (2 lesions) in non-elderly patients and 1% (2) from elderly group. 12 patients had metachronous gastric cancers not considered local recurrences during median 14-month follow-up.	Comparative studies in table 2.
Jang JS, Choi SR, Graham DY et al. (2009) Risk factors for immediate and delayed bleeding associated with endoscopic submucosal dissection of gastric neoplastic lesions. Scandinavian Journal of Gastroenterology 44 (11): 1370–6.	Case series n = 144 Follow-up not reported (not purpose of study)	Bleeding in 22.2% (32 cases) (immediate in 29) Histology of tumour was only factor statistically associated with bleeding (adjusted hazard ratio 6.770, 95% CI 1.830-25.048, p = 0.004)	This event is already reported in table 2.
Jang JS, Choi SR, Qureshi W et al. (2009) Long-term outcomes of endoscopic submucosal dissection in gastric neoplastic lesions at a single institution in South Korea.	Case series n = 402 (107 LGD, 97 HGD, 198 early gastric cancer) Median follow-up = 30 months	En bloc with clear margins: 87.9% (174/198) Local recurrence: 5.1% (10/198) 3-year cancer-free survival: 94.9%	Comparative studies in table 2.

Scandinavian Journal of Gastroenterology 44:1315–22.			
Jee YS, Hwang SH, Rao J et al. (2009) Safety of extended endoscopic mucosal resection and endoscopic submucosal dissection following the Japanese Gastric Cancer Association treatment guidelines. British Journal of Surgery 96: 1157–61.	Case series n = 129 treated with both EMR and ESD Follow-up = not reported	2.3% (3/129) had lymph node metastases. Of the 52 with submucosal cancer, 4% (2/52) had lymph node metastases. There were no lymph node metastases in those with differentiated mucosal cancers without ulcer formation	Larger studies included in table 2.
Jeon SW, Jung MK, Cho CM et al. (2009) Predictors of immediate bleeding during endoscopic submucosal dissection in gastric lesions. Surgical Endoscopy 23: 1974–9.	Case series n = 167 (167 gastric lesions) Follow-up not reported (not purpose of study)	En-bloc resection: 98.2% Immediate bleeding: 12.0% (20/167) Delayed bleeding: 3 (within 24 hours of procedure) Older age and location of lesions (antrum) was associated with lower bleeding frequency.	Larger studies included in table 2.
Jeon SW, Jung MK, Kim SK et al. (2010) Clinical outcomes for perforations during endoscopic submucosal dissection in patients with gastric lesions. Surgical Endoscopy 24:911–6.	Retrospective case series n = analysis of 39 perforations out of 1711 treated for gastric lesions	26 were macroperforations. All but 1 had emergency surgery as a result.	Comparative studies in table 2.
Jeong HK, Park CH, Jun CH et al. (2007) A prospective randomized trial of either famotidine or pantoprazole for the prevention of bleeding after endoscopic submucosal dissection. Journal of Korean Medical Science 22: 1055–9.	RCT n = 176 (85 with pantoprazole vs 79 with famotidine to prevent bleeding after ESD) Follow-up not reported (not purpose of study)	Significantly lower in pantopraxole group (3.5% vs 12.7% [absolute numbers not reported], p = 0.031)	This event is already reported in table 2. Outcomes relate to pharmaceutical agent to prevent bleeding.

Kakushima N, Fujishiro M, Kodashima S et al. (2006) A learning curve for endoscopic submucosal dissection of gastric epithelial neoplasms. Endoscopy 38: 991–5.	Case series n = 383 gastric neoplasms) Follow-up not reported (not purpose of study)	En-bloc with clear margins: 91% (347/383) Perforation: 3.9% Bleeding 3.4% [absolute numbers not reported] No significant difference in efficacy or complications between operators with from 1 to 188 cases in their caseload.	Comparative studies and studies reporting on recurrence in table 2.
Katsube T, Murayama M, Isohata N et al. (2009) The efficacy of endoscopic submucosal dissection compared with modified endoscopic aspiration mucosectomy by assessing the short-term therapeutic results for differentiated mucosal gastric cancer. Anticancer research 29: 4271–4.	Non-randomised comparative study n = 110 (53 ESD vs 57 endoscopic aspiration mucosectomy [a type of EMR with a 2-channel endoscope]) Follow-up not reported	En-bloc resection rate for lesion sizes < 10mm, 11–20 mm, > 20 mm : ESD: 92.3%, 81.8%, 88.2% endoscopic mucosectomy: 86.2%, 61.1%, 10.0% [absolute numbers not reported] By the above lesion sizes, perforations occurred in 1, 2, 0 patients in ESD group and 2, 0 and 0 in the mucosectomy group.	Larger studies included in table 2.
Kim HG, Cho JY, Bok GH et al. (2008) A novel device for endoscopic submucosal dissection, the Fork knife. World Journal of Gastroenterology 14: 6726–32.	Non-randomised comparative study n = 337 (265 lesions with Fork knife vs 72 with Flexknife) Follow-up not reported	En-bloc resection rate: 95.8% (254/265) with Fork knife and 93.1% (67/72) with Flexknife Perforation in 3 cases in each group, all successfully treated with endoscopic clipping and fasting.	Studies with recurrence in table 2.
Kim ES, Jeon SW, Park SY et al. (2009) Where has the tumor gone? The characteristics of cases of negative pathologic diagnosis after endoscopic mucosal resection. Endoscopy 41:739–45.	Retrospective case series n = 20 patients with negative findings after EMR or ESD analysed (out of 633)	Purpose to look at clinical, endoscopic and histological features of gastric tumours with pathologically negative findings at EMR.	Comparative studies in table 2. (Patients treated with ESD and EMR are combined and outcomes not explicitly related to efficacy or safety of the procedure)
Lee TH, Cho JY, Chang YW et al. (2010) Appropriate indications for endoscopic submucosal dissection of early gastric cancer according to tumor size and histologic type. Gastrointestinal Endoscopy 71:920–6.	Retrospective case series n = 461 (487 lesions) Median follow-up = 13.5 months	Curative resection in 88.7% intestinal-type (IT) cancers ≤ 2cm 73.3% in IT cancers > 2cm 37.9% in non-IT cancers Local recurrence after 3 years: 1.5% (2) with small IT, 6.7% (6) in large IT and none in non-IT (after 5 years, none in any group) Metastatic disease in none after 3 or 5 years	Comparative studies in table 2.

Mannen K, Tsunada S, Hara M et al. (2010) Risk factors for complications of endoscopic submucosal dissection in gastric tumors: analysis of 478 lesions. Journal of Gastroenterology 45:30–6.	Retrospective case series n = 436 (478 lesions)	Purpose to look at factors of serious complications. Perforation in 3.6% (17/478) lesions Bleeding in 8.2% (39/478) lesions	Comparative studies in table 2.
Oda I, Gotoda T, Hamanaka H et al. (2005) Endoscopic submucosal dissection for early gastric cancer: Technical feasibility, operation time and complications from a large consecutive series.igestive Endoscopy 17: 54–8.	Case series n = 945 (1033 early gastric cancer lesions) Follow-up not reported	En-bloc resection rate with clear margins: 93% (957/1033) Delayed bleeding in 6% (59/945) of patients (transfusion only required in 1) Perforation during the procedure in 4% (35/945) of patients; all but 1 who required surgery were managed with endoscopic clips	Comparative studies and studies with longer follow-up in table 2.
Ono H (2005) Endoscopic submucosal dissection for early gastric cancer. Chinese Journal of Digestive Diseases 6: 119–21.	Case series n = 488 lesions Median follow-up = 16 months	96% (471/488) en bloc. No recurrence.	Larger studies included in table 2.

Ono H, Hasuike N, Inui T et al. (2008) Usefulness of a novel electrosurgical knife, the insulation-tipped diathermic knife-2, for endoscopic submucosal dissection of early gastric cancer. Gastric Cancer 11: 47–52.	Case series n = 602 lesions Follow-up = not reported	95% en-bloc and margin-free rate for those treated with original knife; 99% with a later version of the knife (not significant) 3.9% perforation with original knife and 5% for newer knife (not significant)	Larger studies included in table 2.
Ono S, Fujishiro M, Niimi K et al. (2009) Technical feasibility of endoscopic submucosal dissection for early gastric cancer in patients taking anti-coagulants or anti-platelet agents. Digestive and Liver Disease 41: 725–8.	Comparative case series n = 408 (444 lesions) Follow-up = 8 weeks	No significant difference in en-bloc resection or perforation rate between patients taking anti-coagulants or anti-platelet agents (en-bloc: 96.4% [54/56] vs 94.3% [366/388] and perforation: 1.8% [1/56] vs 4.4% [17/388])	Larger studies with longer follow-up included in table 2.
Ono S, Kato M, Ono Y et al. (2009) Effects of preoperative administration of omeprazole on bleeding after endoscopic submucosal dissection: a prospective randomised controlled trial. Endoscopy 41: 299–303.	RCT (of different administration of omeprazole) n = 155 (81 preoperative administration, 81 postoperative administration Follow-up not reported	Major bleeding occurred in a patient in the postoperative group. Minor bleeding occurred on day 1 in 6 in the preoperative group and 5 in the postoperative group (not significant).	Larger studies included in table 2.
Onozato Y, Kakizaki S, Ishihara H et al. (2008) Feasibility of endoscopic submucosal dissection for elderly patients with early gastric cancers and adenomas. Digestive Endoscopy 20: 12–6.	Comparative case series (of younger and older patients) n = 226 (251 lesions)	En bloc resection rate with tumour-free margins and complications was not significantly greater in older patients (en-bloc: 96.4% [106/110] vs 95% [134/141], no complications: 84% [101/110] vs 85% [120/141])	Larger studies included in table 2.

Onozato Y, Ishihara H, Iizuka H et al. (2006) Endoscopic submucosal dissection for early gastric cancers and large flat adenomas. Endoscopy 38 (10): 980–6.	Case series n = 160 (171 early gastric cancer) Follow-up not reported	En-bloc resection with clear margins: 94.2% (161/171) Immediate bleeding: 2.9% (5/171) Delayed bleeding: 7.6% (13/171) Perforation: 3.5% (6/171) (all events treated successfully endoscopically)	Larger studies included in table 2.

Probst A, Maerkl B, Bittinger M et al. (2010) Gastric ischemia following endoscopic submucosal dissection of early gastric cancer. Gastric Cancer 13:58–61.	Case report n = 1	Circumferential ischaemia of the sub-cardial and antral gastric mucosa detected at routine endoscopic follow-up 24 hours after ESD. It was accompanied by leukocytosis and abdominal tenderness. Successfully treated conservatively with fasting, antibiotics and PPIs. Antral stenosis developed after 4 weeks – successfully managed with dilatations. Ischaemic event was attributed to the potential combined vasoconstrictive effect of adrenaline injection, combined with sub-mucosal fluid injection as part of the ESD procedure.	Larger studies in table 2.
Shimura T, Sasaki M, Kataoka H et al. (2007) Advantages of endoscopic submucosal dissection over conventional endoscopic mucosal resection. Journal of Gastroenterology & Hepatology 22: 821–6.	Non-randomised comparative study n = 107 (48 EMR vs 59 ESD) Follow-up not reported	En-bloc resection: ESD – 88.1 (52/59) EMR – 31.3% (15/48) ($p < 0.001$) ESD – 1 recurrence (with piecemeal resection) EMR – 6 recurrences (1 en bloc, 5 piecemeal)	Larger studies with longer follow-up included in table 2.
Shimura T, Joh T, Sasaki M et al. (2007) Endoscopic submucosal dissection is useful and safe for intramucosal gastric neoplasms in the elderly. Acta Gastroenterologica Belgica 70: 323–30.	Comparative case series (different age groups) n = 116 (125 lesions) Follow-up = not reported	No significant difference between age groups or tumour sizes in en bloc rate (rates ranged from 77.8% to 92.6%). [absolute numbers not reported] Recurrence in 2 lesions in 2 patients. ESD was performed and no further recurrences in any patients were reported (exact follow-up not reported).	Larger studies included in table 2.
Sohn YJ, Jang JS, Choi SR et al. (2009) Early detection of recurrence after endoscopic treatment for early gastric cancer. Scandinavian Journal of Gastroenterology 44: 1109–14.	Case series n = 212 Follow-up = up to 24 months	Local recurrence: 4.7% (10/212) (study largely about methods to detect recurrence)	Comparative studies in table 2.
Sumida A, Yanai H,	Case report	This occurred after	This outcome is already

Tanioka Y et al. (2008) Stenosis of gastric body as a rare complication after submucosal dissection for multiple gastric epithelial tumours. Journal of Gastrointestinal Cancer 39: 34–6.	n = 1 of stenosis of gastric body	multiple, wide resection 5 times for 4 lesions of early gastric cancer.	reported in table 2.

Takenaka R, Kawahara Y, Okada H et al. (2008) Risk factors associated with local recurrence of early gastric cancers after endoscopic submucosal dissection. Gastrointestinal Endoscopy 68: 887–94.	Case series n = 306 Median follow-up = 26 months	Complete resection: 80.4% (246/306) Bleeding requiring transfusion in 2 (0.65%) Perforation during ESD in 16 (5.2%) (all managed endoscopically).	Comparative studies in table 2.
Takizawa K, Oda I, Gotoda T et al. (2008) Routine coagulation of visible vessels may prevent delayed bleeding after endoscopic submucosal dissection--an analysis of risk factors. Endoscopy 40: 179–3.	Case series n = 968 (1083 early gastric lesions) Follow-up not reported	Delayed bleeding in 5.8% (63 lesions) in 6.5% of patients. Blood transfusion required only in 1. Location in upper third of stomach and use of coagulation were indicators of lower rate of delayed bleeding.	Comparative case series or studies reporting on local recurrence are reported in table 2.
Tsunada S, Ogata S, Mannen K et al. (2008).Case series of endoscopic balloon dilation to treat a stricture caused by circumferential resection of the gastric antrum by endoscopic submucosal dissection. Gastrointestinal Endoscopy 67: 979–3.	Case series n = 532 Follow-up not reported	5 strictures in 5 patients All located in the antrum 1 required surgical intervention but other 4 had balloon dilation (this was successful in 2 but not in 2 since these patients also had gastric perforation)	Outcome reported in table 2.
Uedo N, Takeuchi Y, Yamada T et al. (2007) Effect of a proton-pump inhibitor or an H2-receptor antagonist on prevention of bleeding from ulcer after endoscopic submucosal dissection of early gastric cancer: a prospective randomised controlled trial. American Journal of Gastroenterology 102: 1610–6.	RCT (of methods to prevent bleeding from an ulcer) n = 143 with EGC (73 proton-pump inhibitor vs 70 H2-receptor) Follow-up not reported	Bleeding in 4 in proton-pump inhibitor group and 11 in H2-receptor group (p = 0.057)	Larger studies in table 2.

Watanabe K, Ogata S, Kawazoe S et al. (2006) Clinical outcomes of EMR for gastric tumours: historical pilot evaluation between endoscopic submucosal dissection and conventional mucosal resection. Gastrointestinal Endoscopy 63: 776–82.	Non-randomised comparative study n = 229 (245 lesions: ESD 120, EMR 125) Median follow-up = 6.6 months	Lesions treated with ESD were significantly larger. En-bloc and complete resection significantly greater with ESD (91.7% vs 84% and 87.5% vs 72.8%; p < 0.01). Remnant lesions in 4 (EMR) and 0 (ESD) (lesions ≤ 10 mm) and in 3 (EMR) and 3 (ESD) (of lesions > 10 mm). Perforations in 3.2% (4/125) EMR and 4.2% (5/120) ESD	Comparative studies with more patients and longer follow-up reported in table 2.
Yamaguchi Y, Katusmi N, Aoki K et al. (2007) Resection area of 15 mm as dividing line for choosing strip biopsy or endoscopic submucosal dissection for mucosal gastric neoplasm. Journal of Clinical Gastroenterology 41: 472–6.	Non-randomised comparative study n = 90 lesions (36 strip biopsy EMR vs 54 ESD) Median follow-up = 23 months	Complete resection: 91.6% vs 83.3% (p = 0.25) No significant differences in complication rate. 1 patient in each group had recurrence during follow-up	Comparative studies with more patients reported in table 2.
Yamaguchi N, Isomoto H, Fukuda E et al. (2009) Clinical outcomes of endoscopic submucosal dissection for early gastric cancer by indication criteria. Digestion 80: 173–81.	Case series n = 551 (589 early gastric cancer lesions)	Duplicate reporting of patients as in Isomoto (2009) above	Comparative studies in table 2.

Appendix B: Related NICE guidance for endoscopic submucosal dissection of gastric lesions

Guidance	Recommendations
Interventional procedures	**Endoscopic submucosal dissection of lower gastrointestinal lesions. NICE interventional procedures guidance 335 (2010)** 1.1 Current evidence on endoscopic submucosal dissection (ESD) of lower gastrointestinal lesions shows that it is efficacious, but evidence on long-term survival when used to treat malignant lesions is limited in quantity. There are some concerns about safety with regard to the risk of perforation and bleeding. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research. 1.2 Clinicians wishing to undertake ESD of lower gastrointestinal lesions should take the following actions. • Inform the clinical governance leads in their Trusts. • Ensure that patients understand the uncertainty about the procedure's safety and efficacy in relation to the risks of perforation and bleeding, and that conversion to open surgery may be necessary. Patients should be provided with clear written information. In addition, the use of NICE's information for patients ('Understanding NICE guidance') is recommended (available from www.nice.org.uk/IPG335publicinfo). • Audit and review clinical outcomes of all patients having ESD of lower gastrointestinal lesions (see section 3.1). 1.3 Endoscopic submucosal dissection of lower gastrointestinal lesions is a technically challenging procedure and should only be carried out by clinicians with specific training in the technique. The Joint Advisory Group on Gastrointestinal Endoscopy intends to prepare training standards on this procedure. 1.4 Patient selection should be carried out either by a colorectal surgeon or by both a colorectal surgeon and an endoscopist who are experienced in this technique. 1.5 NICE encourages further research into ESD of lower gastrointestinal lesions. There should be clear documentation of the incidence of complications including perforation, haemorrhage and need for open surgery (with the reasons for this), rates of complete resection, and long-term outcomes including local recurrence and survival. **Laparo-endogastric surgery. NICE interventional procedures guidance 25 (2003)** 1.1 Current evidence on the safety and efficacy of laparo-endogastric surgery does not appear adequate to support the

	use of this procedure without special arrangements for consent and for audit or research. Clinicians wishing to undertake laparo-endogastric surgery should inform the clinical governance leads in their Trusts. They should ensure that patients offered it understand the uncertainty about the procedure's safety and efficacy and should provide them with clear written information. Use of the Institute's Information for the Public is recommended. Clinicians should ensure that appropriate arrangements are in place for audit or research. Publication of safety and efficacy outcomes will be useful in reducing the current uncertainty. NICE is not undertaking further investigation at present. 1.2 The procedure should only be performed by specialists in laparoscopic surgery who have observed at least one patient undergoing the procedure. **Laparoscopic gastrectomy for cancer. NICE interventional procedures guidance 269 (2008)** 1.1 Current evidence on the safety and efficacy of laparoscopic gastrectomy for cancer appears adequate to support the use of this procedure, provided that normal arrangements are in place for clinical governance, consent and audit. 1.2 This procedure is technically demanding. Surgeons undertaking it should have specific training and special expertise in laparoscopic surgical techniques, and should perform their initial procedures with an experienced mentor. 1.3 Patient selection and management should be carried out in the context of a multidisciplinary team with established experience in the treatment of gastric cancer.
Clinical guidelines	**Dyspepsia: Managing dyspepsia in adults in primary care. NICE clinical guideline 17 (2004)** **Interventions for gastro-oesophageal reflux disease (GORD)** • Offer patients who have GORD a full-dose PPI for 1 or 2 months. • If symptoms recur following initial treatment, offer a PPI at the lowest dose possible to control symptoms, with a limited number of repeat prescriptions. **Interventions for peptic ulcer disease** • Offer H. pylori eradication therapy to H. pylori-positive patients who have peptic ulcer disease. • For patients using NSAIDs with diagnosed peptic ulcer, stop the use of NSAIDs where possible. Offer full-dose PPI or H_2 receptor antagonist (H_2RA) therapy for 2 months to these patients and, if *H. pylori* is present, subsequently offer eradication therapy. **Interventions for non-ulcer dyspepsia**

	• Management of endoscopically determined non-ulcer dyspepsia involves initial treatment for *H. pylori* if present, followed by symptomatic management and periodic monitoring.
	• Re-testing after eradication should not be offered routinely, although the information it provides may be valued by individual patients.

Appendix C: Literature search for endoscopic submucosal dissection of gastric lesions

Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	19/05/2010	May 2010
Database of Abstracts of Reviews of Effects – DARE (CRD website)	19/05/2010	N/A
HTA database (CRD website)	19/05/2010	N/A
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	18/12/2009	Issue 4, 2009
MEDLINE (Ovid)	15/12/2009	19/05/2010
MEDLINE In-Process (Ovid)	15/12/2009	19/05/2010
EMBASE (Ovid)	18/12/2009	19/05/2010
CINAHL (NLH Search 2.0 or EBSCOhost)	19/05/2010	N/A
BLIC (Dialog DataStar)	19/05/2010	N/A
National Institute for Health Research Clinical Research Network Coordinating Centre (NIHR CRN CC) Portfolio Database	18/12/2009	None found.
Current Controlled Trials metaRegister of Controlled Trials - mRCT	18/12/2009	None found.
Clinicaltrials.gov	18/12/2009	None found.
Zetoc	19/05/2010	N/a

Websites searched on 18/12/2009
- National Institute for Health and Clinical Excellence (NICE)
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – surgical (ASERNIP-S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- Conference websites
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1	endoscopy/ or exp endoscopy, digestive system/ or exp endoscopy, gastrointestinal/
2	endoscop*.tw.
3	duodenscop*.tw.
4	(endoscop* adj3 gastrointest*).tw.
5	Endoscopes/

6	or/1-5
7	submucos*.tw.
8	Intestinal mucosa/
9	7 or 8
10	exp Dissection/
11	(dissect* or resect*).tw.
12	microdissect*.tw.
13	or/10-12
14	6 and 9 and 13
15	ESD.tw.
16	EMR.tw.
17	14 or 15
18	14 or 16
19	((gastric* or stomach* or duodenal* or duodenum*) adj3 (ulcer* or lesion* or adenoma* or polyp* or dysplas*)).tw.
20	Stomach Ulcer/
21	Duodenal Ulcer/
22	Intestinal Polyps/
23	Gastric Ulcer/
24	Precancerous Conditions/
25	(precancer* or pre-cancer* or pre-malign* or premalign* or preneoplast* or pre-neoplastic*).tw.
26	((early or flat*) adj3 (neoplasm* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan*)).tw.
27	24 or 25 or 26
28	(stomach* or gastric* or duodenal* or duodenum*).tw.
29	27 and 28
30	(neoplasm$ or cancer$ or carcinoma$ or adenocarcinom$ or tumour$ or tumor$ or malignan$).tw.
31	Stomach Neoplasms/
32	Duodenal Neoplasms/
33	Intestinal Neoplasms/

34	28 and 30
35	19 or 20 or 21 or 22 or 23 or 29 or 31 or 32 or 33 or 34
36	35 and 17
37	35 and 18
38	limit 36 to english language
39	limit 37 to english language
40	1999*.ed.
41	2000*.ed.
42	2001*.ed.
43	2002*.ed.
44	2003*.ed.
45	2004*.ed.
46	2005*.ed.
47	2006*.ed.
48	2007*.ed.
49	2008*.ed.
50	2009*.ed.
51	or/40-50
52	38 and 51
53	38 and 51
54	50 or 46 or 47 or 48 or 45 or 49
55	39 and 54
56	38 and 54