

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of endoscopic submucosal dissection of lower gastrointestinal lesions

This procedure can be used to treat abnormalities on the wall of the bowel. A long camera (colonoscope) is inserted into the bowel to view the affected area. A solution is injected into the wall of the bowel, and then the part of the bowel 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 examining the abnormality 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 July 2009.

Procedure name

- Endoscopic submucosal dissection of lower gastrointestinal lesions

Specialty societies

- British Society of Gastroenterology
- The Association of Cancer Physicians (Royal College of Physicians)
- The Association of Coloproctology of Great Britain and Ireland

Description

Indications and current treatment

'Colorectal lesions' may include benign, premalignant and malignant lesions. Many patients with colorectal lesions may be asymptomatic, but some patients may experience blood in the stool, change in bowel habit, abdominal pain and unexplained weight loss.

Depending on clinical presentation and symptom status, lesions may be identified and investigated radiologically (barium enema, computed tomography [CT] colonography) and/or endoscopically. Treatment ideally involves resection of the lesions, and may be performed endoscopically (if the lesion is small and amenable to endoscopic management) or surgically (if the lesion is large and/or has invaded deeper into the bowel wall). In practice, small lesions are often removed endoscopically – without certainty about whether it is malignant or benign and before a biopsy result – to both remove and diagnose the lesion.

Depending on their type, current practice for the management of small colorectal 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. EMR is technically difficult because the walls of the bowel are relatively thin, particularly in the colon, and there is a significant risk of perforation. Sometimes EMR (using a snare) is difficult to perform for thin, laterally spreading lesions, those with a bowel wall abnormality (according to the pit pattern of the colorectal mucosa), and depressed or small lesions located within the submucosa. Also, EMR may be difficult (or impossible) for fibrosed lesions (from previous biopsy or EMR).

The Paris morphological classification system is often used to classify superficial neoplastic lesions of the bowel. Lesions protruding into the bowel are classified as Ip, Ips or Is depending on whether or not they are pedunculated, subpedunculated or sessile. Flat elevated lesions are classified as 0-IIa if they are flat elevations or 0-11a/c if they are flat with a central depression. Flat lesions are classified as 0-IIb if there is flat mucosal change, and as 0-IIc if there is mucosal depression. They are classified as 0-IIc/a if there is mucosal depression with a raised edge.

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 decrease recurrence by removing a more complete specimen and also permits a more accurate histopathological assessment.

Patients may need CT or magnetic resonance imaging as part of the diagnostic work-up before selection for the procedure. Preoperative diagnosis with a biopsy is often done before this procedure is performed. Bowel preparation is used to aid visualisation and to minimise the risk of faecal contamination of the peritoneum in the event of perforation. The procedure is usually performed with the patient under sedation or general anaesthesia. A colonoscope with a transparent hood is inserted through the anus to visualise the lesion. The colonoscope has a transparent hood to make sure it is used safely. Sometimes the colonoscope has a water-jet system to clean the area for increased visibility.

The submucosa is injected with fluid that may contain sodium hyaluronate. This lifts the lesion off the submucosa, making the lesion protrude into the lumen. Included in the submucosal injection may be small quantities of a pigment dye (to help delineate the lesion) and adrenaline (to reduce the risk of bleeding).

An initial circumferential mucosal incision is made with the electrothermal knife around the lesion. Submucosal dissection is then performed under endoscopic visualisation, parallel to the muscle layer. A transparent hood may be used to retract the already dissected part of the lesion out of the field of view.

The electrothermal knife is used to achieve haemostasis. Endoscopic clips may be used to control bleeding and treat small perforations.

List of studies included in the overview

This overview is based on approximately 2550 patients from a systematic review of 14 studies (1314 patients), 1 non-randomised comparative study, 7 case series (including a report of perforations) and one case report.

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.

Efficacy

En bloc lesion resection rates and completeness of resection

A systematic review and meta-analysis of 14 studies including 1314 patients reported an en bloc lesion resection rate of 85% and complete cure (en bloc and histologically clear margins) of 75% (follow-up not stated)¹.

A retrospective comparative study with 536 lesions reported significantly higher rates of en bloc resection in the patients treated with ESD (99%, 463/468) than those treated with simplified ESD using a snare (91%, 40/44) or those treated with small incision EMR (83%, 20/24) ($p < 0.004$ for both)².

Case series not included in the meta-analysis reported en bloc resection rates of 87% (352/405)³, 80% (133/166)⁵, 79% (33/42)⁶, 89% (31/35)⁷, and 90% (263/292)¹¹. In the case series of 292, 42 and 35, en bloc resections included complete margins (classified as R0) in 15% (44/292)¹¹, 74% (31/42)⁶, and 63% (22/35)⁷ of patients, respectively.

Recurrence

A case series of 278 patients reported one case of recurrent rectal intramucosal cancer in one of 38 lesions that were incomplete resections and were followed up for a median of 36 months. This was successfully removed in multiple segments¹¹.

A case series of 400 patients (405 lesions) reported that, of the 145 lesions followed up by colonoscopy, there were 3 cases (2%) of local recurrence at a median follow-up of 20 months³.

A case series of 186 patients (200 lesions) reported that, of the 111 lesions followed up by colonoscopy, there were 2 cases (2%) of local recurrence at a median follow-up of 18 months⁴. One was successfully treated with argon plasma and the other resected by partial colectomy.

The case series of 42 patients reported that there were 2 patients with recurrence (3 lesions) at 6-month follow-up⁶. Both en bloc patients opted for surgical resection.

The case series of 35 patients reported recurrence in one patient in which ESD did not result in an en bloc resection at 2-month follow-up. This was treated with argon plasma coagulation and had no further recurrence at 36-month follow-up.

Survival

The case series of 186 patients reported that all but 1 patient who was followed up at a median of 24 months were alive – 1 patient had died from a coexisting malignant disease 23 months after ESD⁴.

Safety

Perforation

Rates of perforation ranged from 0.3 to 14% in the studies (all but one had rates between 0.3 and 6%)^{2,3,4,5,6,7,8,11}. Most were detected during the procedure and most were treated successfully with endoscopic clip insertion.

A study reported a rate of 5% (27/528) perforations in patients treated with gastrointestinal tract ESD at one centre⁸. Nine of these perforations occurred in the rectum or colon (the total number of patients treated in the colon or rectum was not given so it was not possible to calculate separate rates of perforation for these indications).

Another study reported the rate of colonic perforations at 4 centres treated from periods ranging between 1999 and 2004. Perforations occurred in 14% (6/43) of patients treated with ESD and 0.58% (11/1906), 0.05% (4/8240) and 0.02% (1/4811) of patients treated by EMR, polypectomy and hot biopsy, respectively (differences between ESD to other procedures and EMR to polypectomy and hot snare were significant, $p < 0.0001$)⁹.

Other

The case series of 186 patients reported haematochezia (passage of blood with the stools) requiring emergency colonoscopy to apply endoscopic clips in 1% (2/200) of lesions treated⁴. One occurred on the same day as the procedure and the other occurred 10 days after the procedure.

A case report of a 65-year-old man treated with ESD reported an acute intestinal obstruction 18 hours after the procedure¹⁰. After treatment with intravenous fluid therapy, colonoscopic decompression and aggressive fluid resuscitation, the obstruction started to resolve on the 5th day. There was no evidence of perforation or haemorrhage.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to endoscopic submucosal dissection of lower gastrointestinal lesions. Searches were conducted of the following databases, covering the period from their commencement to 4 December 2009: 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).

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 lower gastrointestinal 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.

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

- Computed tomographic colonography (virtual colonoscopy). NICE interventional procedures guidance 129 (2005). Available from www.nice.org.uk/IPG129

Technology appraisals

- Laparoscopic surgery for colorectal cancer. NICE technology appraisal 105 (2006). Available from www.nice.org.uk/TA105
- Capecitabine and oxaliplatin in the adjuvant treatment of stage III (Dukes' C) colon cancer (2006). Available from www.nice.org.uk/TA100

Clinical guidelines

Published

- Improving outcomes in colorectal cancers. NICE cancer service guidance CSGCC (2004). Available from <http://guidance.nice.org.uk/CSGCC>

Under development

- Diagnosis and management of colorectal cancer. NICE clinical guideline (publication expected July 2011)

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

Abbreviations used: CI, confidence interval; CT, computed topography; ESD, endoscopic submucosal dissection; GI, gastrointestinal tract; LST-NG, laterally spreading tumour, non-granular; LST-G, laterally spreading tumour, granular; m, mucosal; R0, complete resection; R1, incomplete resection; Rx, margins not evaluable; sm, submucosal																																																													
Study details	Key efficacy findings			Key safety findings	Comments																																																								
<p>Puli (2009)¹</p> <p>Systematic review Japan, USA Recruitment period: not reported (search from 1966 to 2008) Study population: patients with colonic polyps (mean size= 30.65 mm) n = 1314 (from 14 studies) Sano 2004 Matsuda 2006 Nakajima 2006 Tanaka 2006 Yamegai 2007 Fujishiro 2006 Fujishiro 2006 Jeong-Sik 2005 Onozato 2007 Fujishiro 2007 Yahagi 2004 Saito 2007 Odajima 2007 Yamamoto 2003 Age: not reported Sex: not reported Study selection</p>	<p>Number of patients analysed: 1314</p> <p>Completeness of resection</p> <table border="1"> <thead> <tr> <th>Study</th> <th>Proportion of en bloc resection (95% CI)</th> <th>Proportion of complete cure* (95% CI)</th> </tr> </thead> <tbody> <tr> <td>Sano 2004</td> <td>0.50 (0.23 – 0.77)</td> <td>Same</td> </tr> <tr> <td>Matsuda 2006</td> <td>0.82 (0.73 – 0.89)</td> <td>Same</td> </tr> <tr> <td>Nakajima 2006</td> <td>1.00 (0.29 – 1.00)</td> <td>Same</td> </tr> <tr> <td>Tanaka 2006</td> <td>1.00 (0.95 – 1.00)</td> <td>0.80 (0.69 – 0.89)</td> </tr> <tr> <td>Yamegai 2007</td> <td>1.00 (0.92 – 1.00)</td> <td>0.90 (0.81 – 0.96)</td> </tr> <tr> <td>Fujishiro 2006</td> <td>0.89 (0.73 – 0.97)</td> <td>0.63 (0.45 – 0.79)</td> </tr> <tr> <td>Fujishiro 2006</td> <td>0.46 (0.33 – 0.60)</td> <td>0.34 (0.22 – 0.48)</td> </tr> <tr> <td>Jeong-Sik 2005</td> <td>0.83 (0.59 – 0.96)</td> <td>0.78 (0.52 – 0.94)</td> </tr> <tr> <td>Onozato 2007</td> <td>0.73 (0.54 – 0.88)</td> <td>0.70 (0.51 – 0.85)</td> </tr> <tr> <td>Fujishiro 2007</td> <td>0.92 (0.87 – 0.95)</td> <td>0.71 (0.64 – 0.77)</td> </tr> <tr> <td>Yahagi 2004</td> <td>0.91 (0.85 – 0.95)</td> <td>0.87 (0.80 – 0.92)</td> </tr> <tr> <td>Saito 2007</td> <td>0.84 (0.78 – 0.89)</td> <td>0.70 (0.63 – 0.76)</td> </tr> <tr> <td>Odajima 2007</td> <td>0.92 (0.87 – 0.95)</td> <td>Same</td> </tr> <tr> <td>Yamamoto 2003</td> <td>0.78 (0.70 – 0.84)</td> <td>Same</td> </tr> <tr> <td>Total</td> <td>0.85 (0.78 – 0.91)</td> <td>0.75 (0.67 – 0.82)</td> </tr> </tbody> </table> <p>*Complete cure defined as en bloc plus histological disease-free margins</p> <p>The pooled proportions were calculated with a random effects model.</p> <p>Subgroup analysis</p> <table border="1"> <thead> <tr> <th>Study size</th> <th>No. of</th> <th>Proportion of en bloc</th> <th>Proportion of complete cure</th> </tr> </thead> <tbody> <tr> <td></td> <td></td> <td></td> <td></td> </tr> </tbody> </table>			Study	Proportion of en bloc resection (95% CI)	Proportion of complete cure* (95% CI)	Sano 2004	0.50 (0.23 – 0.77)	Same	Matsuda 2006	0.82 (0.73 – 0.89)	Same	Nakajima 2006	1.00 (0.29 – 1.00)	Same	Tanaka 2006	1.00 (0.95 – 1.00)	0.80 (0.69 – 0.89)	Yamegai 2007	1.00 (0.92 – 1.00)	0.90 (0.81 – 0.96)	Fujishiro 2006	0.89 (0.73 – 0.97)	0.63 (0.45 – 0.79)	Fujishiro 2006	0.46 (0.33 – 0.60)	0.34 (0.22 – 0.48)	Jeong-Sik 2005	0.83 (0.59 – 0.96)	0.78 (0.52 – 0.94)	Onozato 2007	0.73 (0.54 – 0.88)	0.70 (0.51 – 0.85)	Fujishiro 2007	0.92 (0.87 – 0.95)	0.71 (0.64 – 0.77)	Yahagi 2004	0.91 (0.85 – 0.95)	0.87 (0.80 – 0.92)	Saito 2007	0.84 (0.78 – 0.89)	0.70 (0.63 – 0.76)	Odajima 2007	0.92 (0.87 – 0.95)	Same	Yamamoto 2003	0.78 (0.70 – 0.84)	Same	Total	0.85 (0.78 – 0.91)	0.75 (0.67 – 0.82)	Study size	No. of	Proportion of en bloc	Proportion of complete cure					Not reported	<p>Follow-up issues:</p> <ul style="list-style-type: none"> No information on follow-up given for the studies. <p>Study design issues:</p> <ul style="list-style-type: none"> The purpose of the study was to evaluate the proportion of successful en bloc ESD resections. English and Japanese languages were searched. Data were extracted from two independent authors. The pooled effects were calculated with a random effects model because of the heterogeneity of the studies. Subgroup analysis was done by size of study assuming that expertise required to perform procedures might affect the outcome. This also assumed that >100 lesions reported in a study would indicate better experience with the procedure; however, this may not be a good indication of experience if there are a number of surgeons performing the procedures. <p>Study population issues:</p> <ul style="list-style-type: none"> Study populations were not described. <p>Other issues</p> <ul style="list-style-type: none"> This review included 3 studies which have been included in this table^{4, 7, 12}.
	Study	Proportion of en bloc resection (95% CI)	Proportion of complete cure* (95% CI)																																																										
	Sano 2004	0.50 (0.23 – 0.77)	Same																																																										
	Matsuda 2006	0.82 (0.73 – 0.89)	Same																																																										
	Nakajima 2006	1.00 (0.29 – 1.00)	Same																																																										
	Tanaka 2006	1.00 (0.95 – 1.00)	0.80 (0.69 – 0.89)																																																										
	Yamegai 2007	1.00 (0.92 – 1.00)	0.90 (0.81 – 0.96)																																																										
	Fujishiro 2006	0.89 (0.73 – 0.97)	0.63 (0.45 – 0.79)																																																										
	Fujishiro 2006	0.46 (0.33 – 0.60)	0.34 (0.22 – 0.48)																																																										
	Jeong-Sik 2005	0.83 (0.59 – 0.96)	0.78 (0.52 – 0.94)																																																										
	Onozato 2007	0.73 (0.54 – 0.88)	0.70 (0.51 – 0.85)																																																										
	Fujishiro 2007	0.92 (0.87 – 0.95)	0.71 (0.64 – 0.77)																																																										
	Yahagi 2004	0.91 (0.85 – 0.95)	0.87 (0.80 – 0.92)																																																										
	Saito 2007	0.84 (0.78 – 0.89)	0.70 (0.63 – 0.76)																																																										
	Odajima 2007	0.92 (0.87 – 0.95)	Same																																																										
Yamamoto 2003	0.78 (0.70 – 0.84)	Same																																																											
Total	0.85 (0.78 – 0.91)	0.75 (0.67 – 0.82)																																																											
Study size	No. of	Proportion of en bloc	Proportion of complete cure																																																										

Abbreviations used: CI, confidence interval; CT, computed topography; ESD, endoscopic submucosal dissection; GI, gastrointestinal tract; LST-NG, laterally spreading tumour, non-granular; LST-G, laterally spreading tumour, granular; m, mucosal; R0, complete resection; R1, incomplete resection; Rx, margins not evaluable; sm, submucosal						
Study details	Key efficacy findings				Key safety findings	Comments
criteria: completion of data and inclusion criteria since there was no control arm Technique: ESD Follow-up: not reported Conflict of interest/source of funding: not reported	(patients)	studies	resection (95% CI)	(95% CI)		<ul style="list-style-type: none"> • No safety data were reported. • The study did not make clear if the patients being treated had prediagnosis before treatment.
	<100	9	82.60 (66.45 – 94.22)	71.23 (57.17 – 83.46)		
	>100	5	87.77 (85.5 – 89.84)	79.67 (76.97 – 82.25)		

Abbreviations used: CI, confidence interval; CT, computed topography; ESD, endoscopic submucosal dissection; GI, gastrointestinal tract; LST-NG, laterally spreading tumour, non-granular; LST-G, laterally spreading tumour, granular; m, mucosal; R0, complete resection; R1, incomplete resection; Rx, margins not evaluable; sm, submucosal																																																																			
Study details	Key efficacy findings	Key safety findings	Comments																																																																
<p>Toyonaga (2009)²</p> <p>Non-randomised comparative study</p> <p>Japan</p> <p>Recruitment period: 2002–2008</p> <p>Study population: patients with colorectal lesions (see comments section for wall invasion characteristics)</p> <p>n = 536 lesions (patient numbers not given) (468 ESD vs 44 simplified ESD vs 24 EMR)</p> <p>Age: not reported</p> <p>Sex: not reported</p> <p>Patient selection criteria: lesions without metastases (without deep invasion, no lymph invasion); lesions >20 mm</p> <p>Technique: ESD with diluted sodium hyaluronate injection and water-jet short needle knives, simplified</p>	<p>Number of patients analysed: not stated (536 lesions: 468 vs 44 vs 24)</p> <p>Completeness of resection</p> <p>Overall en bloc complete resection rate:</p> <table border="1"> <thead> <tr> <th></th> <th>ESD</th> <th>Simplified ESD</th> <th>EMR</th> </tr> </thead> <tbody> <tr> <td>ESD</td> <td>98.9% (463/468)</td> <td></td> <td></td> </tr> <tr> <td>Simplified ESD</td> <td>90.9% (40/44)</td> <td></td> <td></td> </tr> <tr> <td>EMR</td> <td>83.3% (20/24)</td> <td></td> <td></td> </tr> </tbody> </table> <p>Differences between ESD and the other groups was significant (p = 0.0005 with simplified ESD and p = 0.004 with EMR).</p> <p>Additional outcomes</p> <table border="1"> <thead> <tr> <th></th> <th>ESD</th> <th>Simplified ESD</th> <th>EMR</th> </tr> </thead> <tbody> <tr> <td>Median tumour size *</td> <td>30 mm</td> <td>17 mm</td> <td>20 mm</td> </tr> <tr> <td>Average specimen size**</td> <td>41 mm</td> <td>26 mm</td> <td>22.5 mm</td> </tr> <tr> <td>Average procedure time***</td> <td>60 min</td> <td>27 min</td> <td>19 min</td> </tr> </tbody> </table> <p>*EMR with SI vs simplified ESD not significant but ESD vs simplified ESD was significant (p < 0.0001).</p> <p>**differences between groups were significant (p = 0.018 between EMR and simplified ESD and p < 0.0001 between ESD and simplified ESD)</p> <p>***procedure time was only significant between ESD and simplified ESD (p < 0.0001)</p>		ESD	Simplified ESD	EMR	ESD	98.9% (463/468)			Simplified ESD	90.9% (40/44)			EMR	83.3% (20/24)				ESD	Simplified ESD	EMR	Median tumour size *	30 mm	17 mm	20 mm	Average specimen size**	41 mm	26 mm	22.5 mm	Average procedure time***	60 min	27 min	19 min	<p>Complications</p> <table border="1"> <thead> <tr> <th></th> <th>No. with post-operative bleeding (%)</th> <th>No. of perforations (%)</th> </tr> </thead> <tbody> <tr> <td>ESD</td> <td>7/468 (1.5)</td> <td>7/468 (1.5)</td> </tr> <tr> <td>Simplified ESD</td> <td>1/44 (2.3)</td> <td>2/44 (4.5)</td> </tr> <tr> <td>EMR</td> <td>0/24 (0)</td> <td>0/24 (0)</td> </tr> </tbody> </table> <p>The difference between ESD and simplified ESD was not significant.</p> <p>Further details of how the complications were managed was not reported.</p>		No. with post-operative bleeding (%)	No. of perforations (%)	ESD	7/468 (1.5)	7/468 (1.5)	Simplified ESD	1/44 (2.3)	2/44 (4.5)	EMR	0/24 (0)	0/24 (0)	<p>Follow-up issues:</p> <ul style="list-style-type: none"> This was not explicitly stated but the outcomes appear to relate to the immediate postoperative period. <p>Study design issues:</p> <ul style="list-style-type: none"> Patients were treated at 2 centres. This was a retrospective study. It is unclear if the resection rate includes the accuracy of margins. <p>Study population issues:</p> <ul style="list-style-type: none"> Wall invasion between groups were: <table border="1"> <thead> <tr> <th></th> <th>ESD</th> <th>Simplified ESD</th> <th>EMR</th> </tr> </thead> <tbody> <tr> <td>Adenoma</td> <td>34.4 (161)</td> <td>50 (22)</td> <td>79.2 (19)</td> </tr> <tr> <td>Mucosal cancer</td> <td>48.5 (227)</td> <td>38.6 (17)</td> <td>20.8 (5)</td> </tr> <tr> <td>Submucosal cancer</td> <td>16.7 (78)</td> <td>11.4 (5)</td> <td>0</td> </tr> <tr> <td>Muscularis propia-invasive cancer</td> <td>0.4 (2)</td> <td>0</td> <td>0</td> </tr> </tbody> </table> <p>(significance not calculated)</p> <ul style="list-style-type: none"> Size of tumours was significant between those treated with ESD and simplified ESD; <p>Other issues</p> <ul style="list-style-type: none"> It was not clear from the study if the patients being treated had prediagnosis before treatment (that is, if they were known to have adenoma/mucosal cancer/submucosal cancer). 		ESD	Simplified ESD	EMR	Adenoma	34.4 (161)	50 (22)	79.2 (19)	Mucosal cancer	48.5 (227)	38.6 (17)	20.8 (5)	Submucosal cancer	16.7 (78)	11.4 (5)	0	Muscularis propia-invasive cancer	0.4 (2)	0	0
	ESD	Simplified ESD	EMR																																																																
ESD	98.9% (463/468)																																																																		
Simplified ESD	90.9% (40/44)																																																																		
EMR	83.3% (20/24)																																																																		
	ESD	Simplified ESD	EMR																																																																
Median tumour size *	30 mm	17 mm	20 mm																																																																
Average specimen size**	41 mm	26 mm	22.5 mm																																																																
Average procedure time***	60 min	27 min	19 min																																																																
	No. with post-operative bleeding (%)	No. of perforations (%)																																																																	
ESD	7/468 (1.5)	7/468 (1.5)																																																																	
Simplified ESD	1/44 (2.3)	2/44 (4.5)																																																																	
EMR	0/24 (0)	0/24 (0)																																																																	
	ESD	Simplified ESD	EMR																																																																
Adenoma	34.4 (161)	50 (22)	79.2 (19)																																																																
Mucosal cancer	48.5 (227)	38.6 (17)	20.8 (5)																																																																
Submucosal cancer	16.7 (78)	11.4 (5)	0																																																																
Muscularis propia-invasive cancer	0.4 (2)	0	0																																																																

Abbreviations used: CI, confidence interval; CT, computed topography; ESD, endoscopic submucosal dissection; GI, gastrointestinal tract; LST-NG, laterally spreading tumour, non-granular; LST-G, laterally spreading tumour, granular; m, mucosal; R0, complete resection; R1, incomplete resection; Rx, margins not evaluable; sm, submucosal			
Study details	Key efficacy findings	Key safety findings	Comments
<p>ESD involved the use of a snare, EMR with a small incision</p> <p>Follow-up: not reported</p> <p>Conflict of interest/source of funding: not reported</p>			

Abbreviations used: CI, confidence interval; CT, computed topography; ESD, endoscopic submucosal dissection; GI, gastrointestinal tract; LST-NG, laterally spreading tumour, non-granular; LST-G, laterally spreading tumour, granular; m, mucosal; R0, complete resection; R1, incomplete resection; Rx, margins not evaluable; sm, submucosal																							
Study details	Key efficacy findings	Key safety findings	Comments																				
<p>Saito (2009)³ Saito (2007)¹²</p> <p>Case series</p> <p>Japan</p> <p>Recruitment period: 2003–2006</p> <p>Study population: patients with flat laterally spreading tumours treated at the National Cancer Centre Hospital, Tokyo</p> <p>Location: rectal (111) or colonic lesions (right colon: 153, left colon: 102, cecum (39); Histopathology: adenoma (101), mucosal and SM 1 (255), SM2 (46), other (3); Appearance: 168 LST-NG, 173 LST-G, 15 depressed, 21 protruded 25 recurrent</p> <p>n = 400 (405 lesions)</p> <p>Mean age: 64 (in earlier publication)</p> <p>Sex: 58% male (in earlier publication)</p>	<p>Number of patients analysed: 400 (405 lesions)</p> <p>Completeness of resection</p> <p>En bloc resection was 87% (352/405).</p> <p>Curative resection rate: 86% (350/405) (numerator not given in study; more details of these non-curative not given)</p> <p>Local recurrence</p> <p>Among those who were followed up by colonoscopy more than six months after treatment (145 lesions), there were 3 cases (2%) of local recurrence at a mean follow-up of 20 months. One of these lesions was reported to have previously been treated by piecemeal resection¹².</p> <p>Other</p> <p>Mean resected specimen size: 40 mm</p> <p>NB: 28 of the 200 treated lesions in the earlier publication (Saito 2007)¹² were judged by the authors not to have been curative, mostly because of histology confirming 'sm2' cancer (submucosal deep cancer). This group includes five sm2 lesions which were diagnosed as such before ESD, but treated non-surgically either because the patients were elderly, or at patient request. This information was not reported in the later publication³.</p> <p>20 of the 28 lesions above were treated by subsequent surgery, 1 by chemoradiotherapy, and 7 did not have any definitive treatment 'because of age-related or other reasons'</p>	<p>Complications</p> <table border="1"> <thead> <tr> <th>Event</th> <th>% of patients</th> </tr> </thead> <tbody> <tr> <td>Death</td> <td>0</td> </tr> <tr> <td>Postoperative bleeding</td> <td>1% (4/405)*</td> </tr> <tr> <td>Colonic-wall perforations</td> <td>3.5% (14/405)**</td> </tr> </tbody> </table> <p>**All detected endoscopically during ESD; all were managed successfully with endoclips except for 1 requiring surgery</p> <p>There have been no delayed perforations.</p> <p>The earlier publication (Saito 2007)¹² performed an analysis of the 10 perforations which had occurred until this period</p> <p>Perforation subanalysis</p> <table border="1"> <thead> <tr> <th colspan="2">Characteristics of the 10 perforations</th> </tr> </thead> <tbody> <tr> <td>Tumour location</td> <td>4 right colon 2 left colon 4 rectal</td> </tr> <tr> <td>Macroscopic type</td> <td>3 LST-NG 7 LST-G</td> </tr> <tr> <td>Ulcer scar</td> <td>5 with ulcer scar</td> </tr> <tr> <td>Tumour depth</td> <td>3 sm1 1 sm2 5 mucosal 1 adenoma</td> </tr> <tr> <td>Treatment</td> <td>9 endoscopic clip 1 surgery</td> </tr> </tbody> </table>	Event	% of patients	Death	0	Postoperative bleeding	1% (4/405)*	Colonic-wall perforations	3.5% (14/405)**	Characteristics of the 10 perforations		Tumour location	4 right colon 2 left colon 4 rectal	Macroscopic type	3 LST-NG 7 LST-G	Ulcer scar	5 with ulcer scar	Tumour depth	3 sm1 1 sm2 5 mucosal 1 adenoma	Treatment	9 endoscopic clip 1 surgery	<p>Follow-up issues:</p> <ul style="list-style-type: none"> Not reported (assumed to be postoperative; 90% (180/200) were followed up for 220 days). <p>Study design issues:</p> <ul style="list-style-type: none"> This includes 2 publications from the same centre with consecutive patients at one centre. Consequently, the later publication includes more patients. The earlier publication of this study (Saito 2007) was included in the systematic review¹. <p>Study population issues:</p> <ul style="list-style-type: none"> Age and sex of patients were not reported in the later publication. Study included a small proportion of patients with known relatively advanced local cancer in whom ESD was preferred to surgery because of balancing operative risk against risk of incomplete resection. <p>Other issues:</p> <ul style="list-style-type: none"> In the first publication, the authors noted the high number of rectal perforations in relation to colonic perforations, despite the rectum having a thicker wall. They stated that this surprisingly high rectal perforation rate may be because they are a training centre so most endoscopists attempt this procedure in rectal lesions first. Prediagnosis was completed with conventional endoscopic examination with indigo carmine dye (this was done before the
Event	% of patients																						
Death	0																						
Postoperative bleeding	1% (4/405)*																						
Colonic-wall perforations	3.5% (14/405)**																						
Characteristics of the 10 perforations																							
Tumour location	4 right colon 2 left colon 4 rectal																						
Macroscopic type	3 LST-NG 7 LST-G																						
Ulcer scar	5 with ulcer scar																						
Tumour depth	3 sm1 1 sm2 5 mucosal 1 adenoma																						
Treatment	9 endoscopic clip 1 surgery																						

Abbreviations used: CI, confidence interval; CT, computed topography; ESD, endoscopic submucosal dissection; GI, gastrointestinal tract; LST-NG, laterally spreading tumour, non-granular; LST-G, laterally spreading tumour, granular; m, mucosal; R0, complete resection; R1, incomplete resection; Rx, margins not evaluable; sm, submucosal			
Study details	Key efficacy findings	Key safety findings	Comments
<p>Patient selection criteria: non-invasiveness based on magnification colonoscopy, LST-NG: > 20 mm and LST-G: > 30 mm and curability (determined from histopathology and tumour margins)</p> <p>Technique: ESD with glycerol and sodium hyaluronate acid injection</p> <p>Follow-up: overall follow-up not reported; however, 36% (145/405) of lesions were assessed by colonoscopy at least 6 months after the procedure.</p> <p>Conflict of interest/source of funding: none</p>			<p>procedure was performed).</p>

Abbreviations used: CI, confidence interval; CT, computed topography; ESD, endoscopic submucosal dissection; GI, gastrointestinal tract; LST-NG, laterally spreading tumour, non-granular; LST-G, laterally spreading tumour, granular; m, mucosal; R0, complete resection; R1, incomplete resection; Rx, margins not evaluable; sm, submucosal																											
Study details	Key efficacy findings	Key safety findings	Comments																								
<p>Isomoto (2009)¹¹</p> <p>Case series</p> <p>Japan</p> <p>Recruitment period: 2001–2008</p> <p>Study population: patients with colorectal lesions</p> <p>Location: rectal (78) or colonic lesions (sigmoid: 43, descending: 23, transverse: 48, ascending: 49, cecum: 51);</p> <p>Histopathology: adenoma (122), intramucosal cancer (143), submucosal invasion (27: SM1 18, SM2 9);</p> <p>Appearance: 62 LST-NG, 178 LST-G</p> <p>n = 278 (292 lesions)</p> <p>Mean age: 69 years</p> <p>Sex: 55% male</p> <p>Patient selection criteria: > 20 mm lesions with fibrotic</p>	<p>Number of patients analysed: 278 (292 lesions)</p> <p>Completeness of resection</p> <table border="1"> <thead> <tr> <th></th> <th>Percentage of lesions</th> </tr> </thead> <tbody> <tr> <td>En bloc resection</td> <td>90.1% (263/292)</td> </tr> <tr> <td>Complete resection</td> <td>79.8% (233/292)</td> </tr> <tr> <td>Incomplete resection</td> <td>20.2% (59/292)</td> </tr> <tr> <td>En bloc resection including:</td> <td></td> </tr> <tr> <td>R0 resection</td> <td>15.1% (44/292)</td> </tr> <tr> <td>R1 (lateral) resection</td> <td>4.1% (12/292)</td> </tr> <tr> <td>R1 (basal) resection</td> <td>0% (0/292)</td> </tr> <tr> <td>Rx (lateral) resection</td> <td>1.0% (3/292)</td> </tr> </tbody> </table> <p>Logistic regression analysis showed that only fibrosis was associated with piecemeal resection (OR 3.67 [95% CI 1.09–12.37], p = 0.04).</p> <p>1% (3/292) lesions could not be evaluated for completeness of resection because of difficulties in histopathological assessment (because of 'burn effect' of piecemeal fragments)</p> <p>Recurrence (220 lesions [182 complete resections and 38 incomplete resections]).</p> <p>There were no recurrences in patients with complete resections during a median follow-up period of 33 months. In the incomplete resection group (median follow-up period 36 months), there was one case of recurrent rectal intramucosal cancer which was removed in multiple segments and later had tumour-free lateral and basal margins.</p>		Percentage of lesions	En bloc resection	90.1% (263/292)	Complete resection	79.8% (233/292)	Incomplete resection	20.2% (59/292)	En bloc resection including:		R0 resection	15.1% (44/292)	R1 (lateral) resection	4.1% (12/292)	R1 (basal) resection	0% (0/292)	Rx (lateral) resection	1.0% (3/292)	<p>Complications</p> <table border="1"> <thead> <tr> <th>Event</th> <th>% of patients</th> </tr> </thead> <tbody> <tr> <td>Perforation</td> <td>8.2% (24/292)*</td> </tr> <tr> <td>Bleeding</td> <td>0.7% (2/292)</td> </tr> </tbody> </table> <p>*22 occurred during or immediately after ESD and were managed conservatively after endoscopic closure with clipping; 2 had delayed perforation (more than 24 hours) which was managed by laparotomy and medical treatment. Multivariate logistic regression analysis showed tumour size and presence of fibrosis were significantly associated with perforation (tumour size: OR 1.04 [95% CI 1.01–1.07] and p = 0.02, fibrosis: OR 9.84 [95% CI 3.06–31.63] and p = 0.0001).</p>	Event	% of patients	Perforation	8.2% (24/292)*	Bleeding	0.7% (2/292)	<p>Follow-up issues:</p> <ul style="list-style-type: none"> Scheduled for 1, 6 and 12 months after ESD and then annually (biopsy specimens taken) <p>Study population issues:</p> <ul style="list-style-type: none"> Patients who were likely to have submucosal invasion were assessed with endoscopic ultrasonography before the procedure. Four patients with massive submucosal invasion were discovered so ESD was not indicated (these patients are not included in the 278 patients in this study). Initial endoscopic ultrasonography failed to detect cancer in 18 cases. Of the 278 patients, 62 patients who had a follow-up period of less than 1 year were excluded from the follow-up analyses. 10 patients had additional surgery after ESD so were also not included in the follow-up analyses. <p>Other issues:</p> <ul style="list-style-type: none"> There was no data on survival reported for these patients.
	Percentage of lesions																										
En bloc resection	90.1% (263/292)																										
Complete resection	79.8% (233/292)																										
Incomplete resection	20.2% (59/292)																										
En bloc resection including:																											
R0 resection	15.1% (44/292)																										
R1 (lateral) resection	4.1% (12/292)																										
R1 (basal) resection	0% (0/292)																										
Rx (lateral) resection	1.0% (3/292)																										
Event	% of patients																										
Perforation	8.2% (24/292)*																										
Bleeding	0.7% (2/292)																										

Abbreviations used: CI, confidence interval; CT, computed topography; ESD, endoscopic submucosal dissection; GI, gastrointestinal tract; LST-NG, laterally spreading tumour, non-granular; LST-G, laterally spreading tumour, granular; m, mucosal; R0, complete resection; R1, incomplete resection; Rx, margins not evaluable; sm, submucosal			
Study details	Key efficacy findings	Key safety findings	Comments
<p>scarring, locally residual or invasive carcinoma with slight submucosal penetration</p> <p>Technique: ESD with solution of 10% glycerine plus 5% fructose in 0.9% solution</p> <p>Median follow-up: 33 months (complete resection group); 36 months (incomplete resection group)</p> <p>Conflict of interest/source of funding: none</p>			

Abbreviations used: CI, confidence interval; CT, computed topography; ESD, endoscopic submucosal dissection; GI, gastrointestinal tract; LST-NG, laterally spreading tumour, non-granular; LST-G, laterally spreading tumour, granular; m, mucosal; R0, complete resection; R1, incomplete resection; Rx, margins not evaluable; sm, submucosal																											
Study details	Key efficacy findings	Key safety findings	Comments																								
<p>Fujishiro (2007)⁴</p> <p>Case series</p> <p>Japan</p> <p>Recruitment period: 2000–2006</p> <p>Study population: patients with preoperative diagnoses of mucosal or slight submucosal invasive (sm1) neoplasms (102 adenomas, 72 noninvasive carcinomas, 26 invasive carcinomas)</p> <p>n = 186 (200 lesions)</p> <p>Age: not reported</p> <p>Sex: not reported</p> <p>Patient selection criteria: 1) >2 cm or on colorectal fold 2) submucosal fibrosis from previous treatment or biopsy 3) invasive carcinoma with slight submucosal penetration</p> <p>Patients with</p>	<p>Number of patients analysed: 186 (200 lesions)</p> <p>Completeness of resection</p> <table border="1"> <thead> <tr> <th></th> <th>Percentage of patients</th> </tr> </thead> <tbody> <tr> <td>En bloc resection</td> <td>91.5% (183/200)</td> </tr> <tr> <td>En bloc resection including:</td> <td></td> </tr> <tr> <td>R0 resection</td> <td>70.5% (141/200)</td> </tr> <tr> <td>R1 (lateral) resection</td> <td>18% (36/200)</td> </tr> <tr> <td>R1 (basal) resection</td> <td>0.5% (1/200)</td> </tr> <tr> <td>Rx (lateral) resection</td> <td>11.5% (23/200)</td> </tr> <tr> <td>Rx (basal) resection</td> <td>0% (0/200)</td> </tr> </tbody> </table> <p>Additional treatment was required in 4 patients. Each had colorectal resection with lymphadenectomy because of tumour depth and/or vessel infiltration.</p> <p>For those in whom an en bloc resection was not possible, piecemeal resection was performed.</p> <p>Local recurrence (n = 111 tumours; 54 adenomas, 42 intramucosal carcinomas, 15 SM1 carcinomas)</p> <p>Two cases (1.8%, 2/111) of local recurrence were obtained on colonoscopy in patients who had multiple-piece resections (because of failed en bloc resection) at a median follow-up of 18 months (range: 12 – 60 months):</p> <ul style="list-style-type: none"> 1 was an LST-G noninvasive carcinoma 2 months after ESD treated with argon plasma coagulation 1 was an LST-G SM1 recurrent carcinoma 21 months after ESD resected by partial colectomy. <p>Survival (n = 77 patients; 53 intramucosal carcinoma, 18 SM1 carcinoma, 6 SM2 or deeper carcinomas; 7 had</p>		Percentage of patients	En bloc resection	91.5% (183/200)	En bloc resection including:		R0 resection	70.5% (141/200)	R1 (lateral) resection	18% (36/200)	R1 (basal) resection	0.5% (1/200)	Rx (lateral) resection	11.5% (23/200)	Rx (basal) resection	0% (0/200)	<p>Complications</p> <p>All patients had minor bleeding during the procedure but haemostasis was achieved in each. There were no cases of massive haemorrhage</p> <table border="1"> <thead> <tr> <th>Event</th> <th>% of patients</th> </tr> </thead> <tbody> <tr> <td>Intraoperative perforation</td> <td>5.5% (11/200)*</td> </tr> <tr> <td>Postoperative perforation 2 days after procedure requiring laparotomy</td> <td>0.5% (1/200)**</td> </tr> <tr> <td>Haematochezia requiring emergency colonoscopy to apply endoclips***</td> <td>1% (2/200)</td> </tr> </tbody> </table> <p>*Managed with conservative medical treatment after endoscopic closure of the perforation</p> <p>**Patient also had diabetes mellitus, hypertension, post-sigmoidectomy and post-left nephrectomy and chronic renal failure with haemodialysis (unknown cause of perforation).</p> <p>***Follow-up: same day as the procedure and 10 days after</p>	Event	% of patients	Intraoperative perforation	5.5% (11/200)*	Postoperative perforation 2 days after procedure requiring laparotomy	0.5% (1/200)**	Haematochezia requiring emergency colonoscopy to apply endoclips***	1% (2/200)	<p>Follow-up issues:</p> <ul style="list-style-type: none"> Not all patients were followed up for recurrence (111 tumours were reported on for recurrence); only 77 patients followed up at mean 24 months. <p>Study design issues:</p> <ul style="list-style-type: none"> The procedures were performed by 2 surgeons experienced in performing ESD for gastric tumours. <p>Study population issues:</p> <ul style="list-style-type: none"> This study may include patients reported in Fujishiro (2006)⁷. Some tumours as little as 6 mm were dissected if they had scarring from previous EMR. <p>Other issues:</p> <ul style="list-style-type: none"> This study was included in the systematic review above¹. The authors state that the delayed perforation was of unknown cause but may have been because of thermal injury or from concurrent diseases. Prediagnosis (determination of eligibility) was performed with chromoendoscopy (with or without magnifying endoscopy) and endoscopic ultrasonography for lesions likely to have invaded the submucosa. Authors mention that they have used ESD for patients with known sm2 cancers because of patient preference or in a palliative fashion – however this study excludes such cases.
	Percentage of patients																										
En bloc resection	91.5% (183/200)																										
En bloc resection including:																											
R0 resection	70.5% (141/200)																										
R1 (lateral) resection	18% (36/200)																										
R1 (basal) resection	0.5% (1/200)																										
Rx (lateral) resection	11.5% (23/200)																										
Rx (basal) resection	0% (0/200)																										
Event	% of patients																										
Intraoperative perforation	5.5% (11/200)*																										
Postoperative perforation 2 days after procedure requiring laparotomy	0.5% (1/200)**																										
Haematochezia requiring emergency colonoscopy to apply endoclips***	1% (2/200)																										

Abbreviations used: CI, confidence interval; CT, computed topography; ESD, endoscopic submucosal dissection; GI, gastrointestinal tract; LST-NG, laterally spreading tumour, non-granular; LST-G, laterally spreading tumour, granular; m, mucosal; R0, complete resection; R1, incomplete resection; Rx, margins not evaluable; sm, submucosal			
Study details	Key efficacy findings	Key safety findings	Comments
<p>carcinoid tumours and invasive carcinomas treated with palliative fashion were excluded this analysis.</p> <p>Technique: ESD with endoscope with water-jet system (no water-jet used for deep proximal lesions); using either 1% 1900 kd hyaluronic solution plus normal saline or 10% glycerine plus 5% fructose and 0.9% saline injection</p> <p>Median follow-up: 24 months (for 77 patients)</p> <p>Conflict of interest/source of funding: not reported</p>	<p>suspected nodal metastasis)</p> <p>All but 1 patient survived at a median follow-up of 24 months; this patient died from a coexisting malignant disease 23 months after ESD.</p> <p>3 patients who were at high risk for nodal metastases who refused further surgical treatment were recurrence free at 10, 11 and 18 months after ESD, respectively.</p>		

Abbreviations used: CI, confidence interval; CT, computed topography; ESD, endoscopic submucosal dissection; GI, gastrointestinal tract; LST-NG, laterally spreading tumour, non-granular; LST-G, laterally spreading tumour, granular; m, mucosal; R0, complete resection; R1, incomplete resection; Rx, margins not evaluable; sm, submucosal									
Study details	Key efficacy findings	Key safety findings	Comments						
<p>Kita (2007)⁵</p> <p>Case series</p> <p>Japan</p> <p>Recruitment period: 1998–2005</p> <p>Study population: patients with early stage neoplastic lesions of the colon n = 166</p> <p>Age: not reported</p> <p>Sex: not reported</p> <p>Patient selection criteria: lesions >20 mm</p> <p>Technique: ESD with sodium hyaluronate injection (after saline injection) including indigo dye and epinephrine</p> <p>Follow-up: not reported</p> <p>Conflict of interest/source of funding: not reported</p>	<p>Number of patients analysed: 166</p> <p>Completeness of resection</p> <p>En bloc resection was obtained in 80% (133) of patients. (this was reported by the authors to be 77% in the study but it is not clear why)</p> <p>Other</p> <p>Mean procedure time was 102 minutes.</p> <p>Mean diameter of lesions was 33 mm.</p> <p>109 lesions were granular and 46 were non-granular</p> <p>Of the 33 lesions which were unable to be resected en bloc, the average size was 37 mm. They were also more of the non-granular type and more likely to be in the sigmoid, transverse and ascending colon than those with successful en bloc resection (exact figures not reported).</p>	<p>Complications</p> <table border="1"> <thead> <tr> <th>Event</th> <th>Patients</th> </tr> </thead> <tbody> <tr> <td>Bleeding requiring further endoscopic examination or clip placement</td> <td>3</td> </tr> <tr> <td>Perforation*</td> <td>7</td> </tr> </tbody> </table> <p>*This was treated endoscopically using clips in 5, laparoscopically in 1 and conservatively in 1.</p>	Event	Patients	Bleeding requiring further endoscopic examination or clip placement	3	Perforation*	7	<p>Follow-up issues:</p> <ul style="list-style-type: none"> This was not reported (assumed to be postoperative outcomes). <p>Study design issues:</p> <ul style="list-style-type: none"> It was not described how many surgeons performed the procedures. It is unclear if the en bloc resection rates include accuracy of margins. <p>Study population issues:</p> <ul style="list-style-type: none"> Types of lesions were not described in the population. <p>Other issues</p> <ul style="list-style-type: none"> It was not clear from the study if the patients being treated had prediagnosis before treatment.
Event	Patients								
Bleeding requiring further endoscopic examination or clip placement	3								
Perforation*	7								

Abbreviations used: CI, confidence interval; CT, computed topography; ESD, endoscopic submucosal dissection; GI, gastrointestinal tract; LST-NG, laterally spreading tumour, non-granular; LST-G, laterally spreading tumour, granular; m, mucosal; R0, complete resection; R1, incomplete resection; Rx, margins not evaluable; sm, submucosal																							
Study details	Key efficacy findings	Key safety findings	Comments																				
<p>Hurlstone (2007)⁶</p> <p>Case series</p> <p>UK</p> <p>Recruitment period: 2004–2006</p> <p>Study population: patients with diagnosis of Paris 0 – II adenomas or LSTs who presented to Royal Hallamshire Hospital in Sheffield n = 42</p> <p>Median age: 68</p> <p>Sex: 64% male</p> <p>Patient selection criteria: neoplastic or LST (G or NG) >20 mm, those with T2 N1 disease, evidence of metastases were excluded.</p> <p>Technique: on-site staging followed by ESD with sodium hyaluronic + adrenaline + indigo carmine</p> <p>Median follow-up: 6 months (36 patients)</p>	<p>Number of patients analysed: 42</p> <p>Completeness of resection</p> <table border="1"> <thead> <tr> <th></th> <th>Percentage of patients</th> </tr> </thead> <tbody> <tr> <td>En bloc resection</td> <td>78.6% (33/42)*</td> </tr> <tr> <td>En bloc resection including:</td> <td></td> </tr> <tr> <td>R0 resection</td> <td>93.9% (31/33) of patients with en bloc resection or 73.8% (31/42) of all patients</td> </tr> <tr> <td>R1 resection</td> <td>17% (7/42)</td> </tr> <tr> <td>Rx resection</td> <td>10% (4/42)</td> </tr> </tbody> </table> <p>*9 were dissected piecemeal so were considered R1 or Rx by definition.</p> <p>Mortality</p> <p>30-day mortality: 0%</p> <p>Recurrence</p> <p>36 of the 42 patients were followed up (median 6 months).</p> <ul style="list-style-type: none"> Of the 36 patients followed-up, 2 patients had 3 recurrent lesions. Both patients elected surgical resection, and the post-operative pathology was consistent with focal adenocarcinoma within a dysplastic adenoma (high grade dysplasia tubulovillous adenoma).en bloc 		Percentage of patients	En bloc resection	78.6% (33/42)*	En bloc resection including:		R0 resection	93.9% (31/33) of patients with en bloc resection or 73.8% (31/42) of all patients	R1 resection	17% (7/42)	Rx resection	10% (4/42)	<p>Complications</p> <table border="1"> <thead> <tr> <th>Event</th> <th>Patients</th> </tr> </thead> <tbody> <tr> <td>Uncomplicated bleeding</td> <td>5*</td> </tr> <tr> <td>Perforation**</td> <td>1</td> </tr> <tr> <td>Prolonged hospital stay because of ileus</td> <td>3</td> </tr> </tbody> </table> <p>*4 were 'procedural' and one 'delayed'; all were successfully controlled with endoclips; there were no significant differences in bleeding complications between the different types of lesions</p> <p>**Detected after ESD with palpable cervical subcutaneous emphysema; successfully closed with endoclips; extended right haemocolectomy was completed at the request of the patient to prevent local nodal disease and tumour shedding.</p>	Event	Patients	Uncomplicated bleeding	5*	Perforation**	1	Prolonged hospital stay because of ileus	3	<p>Follow-up issues:</p> <ul style="list-style-type: none"> 36/42 patients completed median of 6 months' surveillance. The other 6 patients did not have ≥1 surveillance so were excluded from the final analysis (reason for loss to follow-up not stated). A later publication of this same study (Hurlstone 2008 in appendix A) reported on 30 patients (which appear to come from these 42 patients) with up to 9 months' follow-up. <p>Study design issues:</p> <ul style="list-style-type: none"> This study was a prospective case series. It was performed to assess the technical feasibility of cap-assisted ESD. <p>Study population issues:</p> <ul style="list-style-type: none"> Of 56 patients considered for ESD, 14 were excluded based on the exclusion criteria. <p>Other issues</p> <ul style="list-style-type: none"> This is one of the few studies published on a UK population. This is the reason for inclusion in this table. All patients had undergone a previous colonoscopic assessment for initial diagnosis.
	Percentage of patients																						
En bloc resection	78.6% (33/42)*																						
En bloc resection including:																							
R0 resection	93.9% (31/33) of patients with en bloc resection or 73.8% (31/42) of all patients																						
R1 resection	17% (7/42)																						
Rx resection	10% (4/42)																						
Event	Patients																						
Uncomplicated bleeding	5*																						
Perforation**	1																						
Prolonged hospital stay because of ileus	3																						

Abbreviations used: CI, confidence interval; CT, computed topography; ESD, endoscopic submucosal dissection; GI, gastrointestinal tract; LST-NG, laterally spreading tumour, non-granular; LST-G, laterally spreading tumour, granular; m, mucosal; R0, complete resection; R1, incomplete resection; Rx, margins not evaluable; sm, submucosal			
Study details	Key efficacy findings	Key safety findings	Comments
Conflict of interest/source of funding: study was funded by The Smith and Nephew Research Foundation, Bardhan Research and Education Trust Research Foundation, Butterfield 'Sasakawa' Foundation (UK), Mason Medical Research Foundation and the Peel Research Foundation.			

Abbreviations used: CI, confidence interval; CT, computed topography; ESD, endoscopic submucosal dissection; GI, gastrointestinal tract; LST-NG, laterally spreading tumour, non-granular; LST-G, laterally spreading tumour, granular; m, mucosal; R0, complete resection; R1, incomplete resection; Rx, margins not evaluable; sm, submucosal																							
Study details	Key efficacy findings	Key safety findings	Comments																				
<p>Fujishiro (2006)⁷</p> <p>Case series</p> <p>Japan</p> <p>Recruitment period: 2001–2005</p> <p>Study population: patients with preoperative diagnosis of large intraepithelial rectal neoplasia with submucosal fibrosis, located on rectal folds, or > 2 cm</p> <p>n = 35</p> <p>Age: not reported</p> <p>Sex: not reported</p> <p>Technique: ESD + hyaluronic acid + saline or 10% glycerine + 5% fructose + saline; after 2004 the submucosal injection included epinephrine + indigo carmine</p> <p>Mean follow-up: 36 months</p> <p>Conflict of</p>	<p>Number of patients analysed: 35</p> <p>Completeness of resection</p> <table border="1"> <thead> <tr> <th></th> <th>Upper rectum (n = 21)</th> <th>Lower rectum (n = 14)</th> <th>Whole rectum (n = 35)</th> </tr> </thead> <tbody> <tr> <td>En bloc resection</td> <td>18 (85.7%)</td> <td>13 (92.9%)</td> <td>31 (88.6%)</td> </tr> <tr> <td>R0 resection</td> <td>16 (76.2%)</td> <td>6 (42.9%)</td> <td>22 (62.9%)</td> </tr> <tr> <td>R1*</td> <td>2 (9.5%)</td> <td>7 (50.0%)</td> <td>9 (25.7%)</td> </tr> <tr> <td>Rx</td> <td>3 (14.3%)</td> <td>1 (7.1%)</td> <td>4 (11.4%)</td> </tr> </tbody> </table> <p>*Extending to the lateral margins (there were none extending to the basal margins)</p> <p>*The R0 resection rate was significantly lower in the lower rectum (p < 0.05).</p> <p>For those in whom an en bloc resection was not possible, piecemeal resection was performed.</p> <p>Recurrence</p> <p>The study authors mention that 3 patients had 'abdominal surgery' during follow-up but no details about the reason are described.</p> <p>1 tumour was detected 2 months after piecemeal dissection. It was treated with argon plasma coagulation and there was no further recurrence during a follow-up period of 36 months.</p> <p>Of 32 tumours (excluding 3 which had abdominal surgery and the case above) there was no recurrence at a mean follow-up of 36 months.</p>		Upper rectum (n = 21)	Lower rectum (n = 14)	Whole rectum (n = 35)	En bloc resection	18 (85.7%)	13 (92.9%)	31 (88.6%)	R0 resection	16 (76.2%)	6 (42.9%)	22 (62.9%)	R1*	2 (9.5%)	7 (50.0%)	9 (25.7%)	Rx	3 (14.3%)	1 (7.1%)	4 (11.4%)	<p>Complications</p> <p>Perforations which were successfully managed conservatively with endoclip after endoscopic closure occurred in 5.7% (2/35) of patients.</p> <ul style="list-style-type: none"> 1 patient had LST adenoma that was 5 cm; perforation (<2 mm) occurred in the lower rectum during ESD. 1 patient had LST adenoma that was 2.5 cm in size in the upper rectum. <p>There was minor bleeding in all patients (mean loss of haemoglobin: 0.5 g/dl) but haemoglobin levels dropped more than 1 g/dl in only 28.6% (10/35) of patients. Transfusion was not required in any patients.</p>	<p>Follow-up issues:</p> <ul style="list-style-type: none"> This study has the longest mean follow-up in all studies retrieved and this is why it was included in this table. <p>Study design issues:</p> <ul style="list-style-type: none"> The submucosal injection technique changed after 2004 due to 'technological advances' (the missing ratio changed from 1:3 to 1:7). The procedure was described as ESD but also described the use of a snare for the initial mucosal incision. <p>Study population issues:</p> <ul style="list-style-type: none"> These patients may have been included in Fujishiro (2007)⁴. It is not stated why 3 patients required abdominal surgery. <p>Other issues:</p> <ul style="list-style-type: none"> This study was also included in the systematic review reported above¹. The authors noted that the R0 resection rate in the lower rectum was quite low; they suggested that this may be due to anatomical reasons and minimal cutting in this area to avoid pain after surgery. Prediagnosis was determined by chromoendoscopy with or without magnifying endoscopy.
	Upper rectum (n = 21)	Lower rectum (n = 14)	Whole rectum (n = 35)																				
En bloc resection	18 (85.7%)	13 (92.9%)	31 (88.6%)																				
R0 resection	16 (76.2%)	6 (42.9%)	22 (62.9%)																				
R1*	2 (9.5%)	7 (50.0%)	9 (25.7%)																				
Rx	3 (14.3%)	1 (7.1%)	4 (11.4%)																				

Abbreviations used: CI, confidence interval; CT, computed topography; ESD, endoscopic submucosal dissection; GI, gastrointestinal tract; LST-NG, laterally spreading tumour, non-granular; LST-G, laterally spreading tumour, granular; m, mucosal; R0, complete resection; R1, incomplete resection; Rx, margins not evaluable; sm, submucosal			
Study details	Key efficacy findings	Key safety findings	Comments
interest/source of funding: none declared			

Abbreviations used: CI, confidence interval; CT, computed topography; ESD, endoscopic submucosal dissection; GI, gastrointestinal tract; LST-NG, laterally spreading tumour, non-granular; LST-G, laterally spreading tumour, granular; m, mucosal; R0, complete resection; R1, incomplete resection; Rx, margins not evaluable; sm, submucosal															
Study details	Key efficacy findings	Key safety findings	Comments												
<p>Fujishiro (2006)⁸</p> <p>Case series</p> <p>Japan</p> <p>Recruitment period: 2000–2005</p> <p>Study population: patients with node-negative cancer or premalignant neoplasia (as predicted preoperatively) in the colon or rectum who had perforations related to ESD (of 27 including perforations in oesophagus and stomach, 2 were adenoma, 16 were mucosal and 9 were submucosal; also, 7 had submucosal fibrosis).</p> <p>n = 9 perforations</p> <p>Of the 27 with perforations: Mean age: 65 Sex: 85% male</p> <p>Technique: ESD</p>	<p>Number of patients analysed: Of the 528 patients treated at the centre by ESD for oesophageal, gastric, colonic and rectal neoplasms, 27 had perforations and data on these 27 patients was reported in this study. The total number of patients treated was not separated out by location of lesions so it is difficult to extract perforation rates from this study.</p> <p>Occurrence of perforation</p> <p>Perforation was identified on plain chest or abdominal radiographs with air accumulation in the abdomen, retroperitoneum or mediastinum (routine for all patients) and endoscopic observation during the procedure of other organs, extraluminal fat, or extraluminal space (even if air was not present).</p> <table border="1"> <thead> <tr> <th>Location</th> <th>No. of perforations</th> </tr> </thead> <tbody> <tr> <td>Oesophageal</td> <td>4</td> </tr> <tr> <td>Gastric</td> <td>14</td> </tr> <tr> <td>Colonic</td> <td>7</td> </tr> <tr> <td>Rectal</td> <td>2</td> </tr> <tr> <td>Total</td> <td>27</td> </tr> </tbody> </table> <p>(For 3 patients with gastric perforations, it was not possible to determine when the perforation occurred. It is not clear from the study when the perforations for the additional 3 patients were identified. Of the other perforations, 87.5% [21/24] occurred during ESD.)</p> <p>Description of perforations</p> <p>All perforations were managed during ESD with endoclips (mean 3 endoclips) when identified immediately and the procedure was continued in all cases. Mean perforation size was 5 mm.</p> <p>The patients were then treated conservatively or surgically. Those with perforations identified after the procedure were usually considered for surgical repair.</p> <p>Recurrence</p> <p>18 of the neoplasms (including those in the colon and rectum) had not recurred after a median follow-up period of 36 months (range 9 – 52).</p> <p>Taku (2007)⁹ reported the following rates of perforation in another audit of patients treated with colonoscopy at 4 other Japanese centres in a period ranging from 1999 to 2004. This included a total 15160 patients, 43</p>	Location	No. of perforations	Oesophageal	4	Gastric	14	Colonic	7	Rectal	2	Total	27		<p>Study design issues:</p> <ul style="list-style-type: none"> This is an audit of one Japanese centre's audit of perforations from ESD for the entire GI tract. The overall perforation rate is 5% (27/528) but the total number of patients treated was not separated out by lesion so it is difficult to extract perforation rates for the colon and rectum. <p>Study population issues:</p> <ul style="list-style-type: none"> Outcomes were presented for all 27 patients (including oesophageal and gastric tumours) so it is difficult to know the exact nature of the colonic and rectal lesions/perforations. <p>Other issues:</p> <ul style="list-style-type: none"> The literature search was limited to publications after 2004 to retrieve evidence on more current versions of the technique. These rates of perforation may reflect earlier versions of the procedure. It was not clear from the study if or how prediagnosis was completed before the procedure was performed.
Location	No. of perforations														
Oesophageal	4														
Gastric	14														
Colonic	7														
Rectal	2														
Total	27														

Abbreviations used: CI, confidence interval; CT, computed topography; ESD, endoscopic submucosal dissection; GI, gastrointestinal tract; LST-NG, laterally spreading tumour, non-granular; LST-G, laterally spreading tumour, granular; m, mucosal; R0, complete resection; R1, incomplete resection; Rx, margins not evaluable; sm, submucosal			
Study details	Key efficacy findings	Key safety findings	Comments
Median follow-up: 36 months	treated by ESD. These rates were reported by the chief of endoscopy at each centre.		
Conflict of interest/source of funding: none	Treatment	No. of perforations	
	Hot biopsy	0.02% (1/4811)	
	Polypectomy	0.05% (4/8240)	
	EMR	0.58% (11/1906)	
	ESD	14% (6/43)	
	Total	0.15% (23/15160)	

Abbreviations used: CI, confidence interval; CT, computed topography; ESD, endoscopic submucosal dissection; GI, gastrointestinal tract; LST-NG, laterally spreading tumour, non-granular; LST-G, laterally spreading tumour, granular; m, mucosal; R0, complete resection; R1, incomplete resection; Rx, margins not evaluable; sm, submucosal			
Study details	Key efficacy findings	Key safety findings	Comments
<p>Park (2008)¹⁰</p> <p>Case report</p> <p>Korea</p> <p>Recruitment period: not reported</p> <p>Study population: 65-year old male with a LST at the caecal base n = 1</p> <p>Technique: ESD with sodium hyaluronate injection</p> <p>Median follow-up: postoperatively</p> <p>Conflict of interest/source of funding: not reported</p>	<p>Report of safety event:</p> <p>A 65 year old male with a LST of 40 mm developed an acute intestinal obstruction 18 hours after ESD was performed. The patient reported 'abdominal fullness' after a morning meal and presented with a distended abdomen with increased bowel sounds with no localised tenderness. There was luminal narrowing from the terminal ileum to the caecum and the proximal bowel had fluid-filled dilatation (determined on CT scan). The patient was treated with intravenous fluid therapy and did not eat anything and developed hypotension and oliguria on the 3rd day. Colonoscopic decompression and aggressive fluid resuscitation and intravenous vasopressors were given on the 4th day but the obstruction remained. On the 5th day, the obstruction started to resolve as liquid and flatulence. There were multiple ulcers with swollen mucosa discovered by diagnostic colonoscopy but there was no evidence of perforation or haemorrhage.</p>		

Validity and generalisability of the studies

- The evidence consists mainly of case series. There is currently no published evidence directly comparing effectiveness or safety of the procedure with other interventions. However, an audit of perforations has included the rate of perforation for ESD in the bowel along with rates of perforation for other procedures to treat the lower GI tract⁹.
- Pre-ESD diagnostic work-up and patient selection criteria tends to be defined inadequately (or not at all) in the reviewed papers, which are concerned mostly with aspects of technical efficacy and safety. Most of the studies describe the use of preoperative chromoendoscopy for prediagnosis of the lesions.
- Some studies report data or mention (without including data) the use of the procedure 'by choice' in patients with deeper/invading small lesions which would have ideally been treated surgically. However, the majority of the evidence relates to pre-diagnosed lesions thought in principle to be dissectable with clear margins through ESD.
- The longest follow-up was a case series of 35 with a mean follow-up of 36 months⁷.
- Most studies published are from Japan and the results may not be generalisable to a UK setting or population. Consequently, despite smaller numbers reported, a publication from the UK was included in the main data extraction table⁶.
- There are some variations in the use of the procedure, particularly related to the instruments used. Most studies use sodium hyaluronate for the submucosal injection. Some studies also include indigo dye and adrenaline in the injection^{3,6,7}. The publication from Saito (2009)³, the earlier patients treated in studies published by Fujishiro, and those included in the study by Isomoto were injected with submucosal solutions including glycerol and fructose^{4,7,11}.
- In order to manage the volume of search results, studies reporting on fewer than 20 patients (not reporting important safety events) and publications before 2004 were excluded. Literature searches were restricted to papers

published after 2003 to help focus on evidence using current versions of the technique; however, the literature suggests that the technique has had further significant evolution since 2004. Consequently, it may be difficult to compare success rates between studies published in 2004 and those published in 2009.

- Most literature reported en bloc resection rates. Some included lesion recurrence rates.
- There were two studies which reported on the rates of perforation at various centres. One reported the perforation rates at one Japanese centre and the other reported rates at four other Japanese centres^{8,9}.
- There appears to be some uncertainty in the literature about the appropriate postoperative care of these patients (that is, which drugs to use to prevent bleeding).

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.

Dr Pradeep Bhandari (British Society of Gastroenterology and Royal College of Physicians), Dr Noriko Suzuki (British Society of Gastroenterology).

- Both Advisers perform this procedure regularly and have performed clinical research on this procedure.
- Less than 10% of specialists are engaged in this area of work, but there is much enthusiasm for this procedure so this could change in the near future.
- Both Specialist Advisers agree that it is a novel procedure of uncertain safety and efficacy. One Specialist Adviser commented that it is now standardised for the upper GI tract in Japan where it was invented; however, it is still considered controversial in the lower GI tract because of a higher rate of complications.
- They considered comparator procedures to include EMR, transanal endoscopic micro-surgery (TEMS), transanal resection of rectal polyps (TART or ETAR) and laparoscopic or open surgery.

- Both Specialist Advisers agreed that training is required which should include observation, familiarisation with equipment, practice on animal models and under supervision of experts. It was highlighted that proper training courses must be established which include practice on animal models.
- The procedure must be done with special ESD knives in special endoscopy rooms. It must be done only in specialist centres by very experienced EMR colonoscopists (over 100 EMRs). One Specialist Adviser highlighted that there are a wide variety of knives with a variety of diathermy settings which can cause some confusion.
- One of the Specialist Advisers commented that the hospital where they work has been prospectively collecting data on the procedure.
- One Specialist Adviser highlighted that patient and lesion selection are currently variable. Patients suitable for this procedure are not being treated because the availability of the procedure is limited.

Efficacy

- Key efficacy outcomes included one-piece resection rate (providing a definitive histological specimen), complete resection rate with clear margins, endoscopic cure rate, clinical cure rate and avoidance of surgery.
- One Specialist Adviser commented that the procedure takes longer than EMR since it is more technically demanding. It also appears to be more expensive than EMR, though, if an en bloc dissection is achieved, less follow-up is needed so less costs are incurred in the long term.

Safety

- The Specialist Advisers included delay in surgery because of slow healing of the polypectomy ulcer and transient abdominal pain during the procedure as anecdotal adverse events.
- Theoretical adverse events include unnecessary surgery and conversion of a curable cancer to an incurable cancer because of perforation.
- A Specialist Adviser highlighted that this procedure is best done by experts to avoid unnecessary surgery. The risk of complication increases significantly in the hands of inexperienced surgeons. Since there are not many UK training

facilities for this procedure, most endoscopists are observing this procedure outside of the UK and attempting it on UK patients without a dedicated training programme.

Patient Commentators' opinions

NICE's Patient and Public Involvement Programme were unable to obtain patient commentary for this procedure.

Issues for consideration by IPAC

- Both this procedure and EMR are also used in other parts of the GI tract.
- There are a variety of techniques used for this procedure, for example, the voltage of the knife and the use of adrenaline and pigment dye in the submucosal injection.
- See above 'validity and generalisability' section.

References

1. Puli SR, Kakugawa Y, Saito Y et al. (2009) Successful complete cure en bloc resection of large nonpedunculated colonic polyps by endoscopic submucosal dissection: a meta-analysis and systematic review. *Annals of Surgical Oncology* 16(8): 2147–51
2. Toyonaga T, Man I, Morita Y et al. (2009) The new resources of treatment for early stage colorectal tumors: Emr with small incision and simplified endoscopic submucosal dissection. *Digestive Endoscopy* 21 (SUPPL. 1) S31–S37
3. Saito Y, Sakamoto T, Fukunaga S et al. (2009) Endoscopic submucosal dissection (ESD) for colorectal tumors. *Digestive Endoscopy* 21 (SUPPL. 1) S7–S12
4. Fujishiro M, Yahagi N, Kakushima N et al. (2007) Outcomes of Endoscopic Submucosal Dissection for Colorectal Epithelial Neoplasms in 200 Consecutive Cases. *Clinical Gastroenterology and Hepatology* 5(6): 678–83
5. Kita H, Yamamoto H, Miyata T et al. (2007) Endoscopic submucosal dissection using sodium hyaluronate, a new technique for en bloc resection of a large superficial tumor in the colon. *Inflammopharmacology* 15(3): 129–31
6. Hurlstone, DP, Atkinson R, Sanders DS et al. (2007) Achieving R0 resection in the colorectum using endoscopic submucosal dissection. *British Journal of Surgery* 94(12): 1536–42
7. Fujishiro M, Yahagi N, Nakamura M et al. (2006) Endoscopic submucosal dissection for rectal epithelial neoplasia. *Endoscopy* 38(5): 493–7
8. Fujishiro M, Yahagi N, Kakushima N et al. (2006) Successful nonsurgical management of perforation complicating endoscopic submucosal dissection of gastrointestinal epithelial neoplasms. *Endoscopy* 38(10): 1001–6
9. Taku K, Sano Y, Fu KI et al. (2007) Iatrogenic perforation associated with therapeutic colonoscopy: a multicenter study in Japan. *Journal of Gastroenterology and Hepatology* 22(9): 1409–14
10. Park SY, Jeon SW. (2008) Acute intestinal obstruction after endoscopic submucosal dissection: report of a case. *Diseases of the Colon & Rectum* 51(8): 1295–7

11. Isomoto H, Nishiyama H, Yamaguchi N et al. (2009) Clinicopathological factors associated with clinical outcomes of endoscopic submucosal dissection for colorectal epithelial neoplasms. *Endoscopy* 41: 679–683
12. Saito Y, Uraoka T, Matsuda T et al. 2007) Endoscopic treatment of large superficial colorectal tumors: a case series of 200 endoscopic submucosal dissections (with video). *Gastrointestinal Endoscopy* 66(5): 966–73

Appendix A: Additional papers on endoscopic submucosal dissection of lower gastrointestinal 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
Chou YP, Saito Y, Matsuda T et al. (2009) Novel diagnostic methods for early-stage squamous cell carcinoma of the anal canal successfully resected by endoscopic submucosal dissection. <i>Endoscopy</i> 41 Suppl-5:2009	Case report n = 1 Follow-up = 23 months	Description of ESD in a patient. No malignancy at 23-month follow-up.	Larger studies in table 2.
Fujishiro M, Yahagi N, Nakamura M et al. (2006) Successful outcomes of a novel endoscopic treatment for GI tumors: endoscopic submucosal dissection with a mixture of high-molecular-weight hyaluronic acid, glycerin, and sugar. <i>Gastrointestinal Endoscopy</i> 63(2): 243–9	Case series n = 30 Follow-up = 1 year	En bloc resection rate: 94% (63/67), histologic en bloc resection rate: 78% (52/67). 1 perforation in a tumour with severe fibrosis managed with endoclipping. One rectal tumour required endoscopic haemostasis from postoperative bleeding.	Larger studies in table 2.
Fusaroli P, Grillo A, Zanarini S et al (2009) Usefulness of a second endoscopic arm to improve therapeutic endoscopy in the lower gastrointestinal tract. Preliminary experience - a case series. <i>Endoscopy</i> 41 (11) 997-1000	Case series n = 8 Follow-up = 12.3 months	Description of slightly different technique (with home-made devices). En-bloc in 7/8. No recurrence at mean 12.3 months.	Larger studies in table 2.
Hurlstone DP, Shorhouse AJ, Brown SR et al. (2008) Salvage endoscopic submucosal dissection for residual or local recurrent intraepithelial neoplasia in the colorectum: a prospective analysis. <i>Colorectal Disease</i> 10(9): 891–7	Case series n = 30 Follow-up = 3–18 months	Index R0 resection rate: 83% (25/30). Overall cure rate: 96% at median 6/12 months. No perforations were reported.	Larger studies in table 2.
Hurlstone DP, Atkinson R, Sanders DS et al. (2006) "Salvage" endoscopic mucosal resection in the colon using a retroflexion gastroscope dissection technique: a prospective analysis. <i>Endoscopy</i> 38: 902–6	Case series n = 76 Follow-up = 24 months (61 patients)	Cure rate after 24 months of follow-up was 98% (60/61).	Unable to determine from study which patients were treated with EMR and which were treated with ESD.

Kobayashi, N, Saito Y, Uraoka T, Matsuda T, Suzuki H, and Fujii T. (2009) Treatment strategy for laterally spreading tumors in Japan: before and after the introduction of endoscopic submucosal dissection. <i>Journal of Gastroenterology & Hepatology</i> 24 (8) 1387-1392	Comparative case series n = 166 lesions	Retrospective comparison EMR only before 2003 and after 2003, ESD \geq 20 mm and EMR for smaller. En-bloc resection pre-2003: 35.0 (14/40), post 2003: 76.5% (75/98).	Larger studies in table 2.
Moon JH, Kim JH, Park CH et al. (2006) Endoscopic submucosal resection with double ligation technique for treatment of small rectal carcinoid tumors. <i>Endoscopy</i> 38(5): 511–14	Case report n = 1	Description of perforation repaired with a band device.	This event is reported in table 2.
Oh TH, Jung HY, Choi KD et al. (2009) Degree of healing and healing-associated factors of endoscopic submucosal dissection-induced ulcers after pantoprazole therapy for 4 weeks. <i>Digestive Diseases & Sciences</i> 54(7): 1494–9	Case series n = 62	Healing of ESD-induced ulcers was dependent on ulcer size. 10.7% complication rate.	This study included patients with gastric cancer. Other studies with more patients and longer follow-up are included in table 2.
Onozato Y, Kakizaki S, Ishihara H et al. (2007) Endoscopic submucosal dissection for rectal tumors. <i>Endoscopy</i> 39(5): 423–7	Case series n = 35 Follow-up = 25.7 months	One-piece resection rate with tumour-free margins was achieved in all but 9 patients. 2.9% (1) perforation rate	Larger studies in table 2.
Repici A, Conio M, De Angelis C et al. (2007) Insulated-tip knife endoscopic mucosal resection of large colorectal polyps unsuitable for standard polypectomy. <i>American Journal of Gastroenterology</i> 102(8): 1617–23	Case series n = 29 Follow-up = 15.7 months	En bloc resection rate: 55.1% (16/29). 1 perforation, 1 intraprocedural arterial bleeding, 1 severely delayed bleeding requiring transfusion, 2 postpolypectomy syndrome from thermal injury	Larger studies in table 2.
Saito Y, Matsuda T, Kikuchi T et al. (2007) Successful endoscopic closures of colonic perforations requiring abdominal decompression after endoscopic mucosal resection and endoscopic submucosal dissection for early colon	Case report n = 2	2 reports of perforation (one for EMR and one for ESD) managed with an endoclip.	This event is reported in table 2.

cancer. Digestive Endoscopy OL 19; Suppl 1: S39			
Sano Y, Saitoh Y. (2007) Risk management of therapeutic colonoscopy (Hot biopsy, polypectomy, endoscopic mucosal resection and endoscopic submucosal dissection). Digestive Endoscopy OL 19; Suppl 1: S25	Case series n = 129 lesions	3% (5) perforation rate all successfully managed conservatively	Larger studies in with longer follow-up are included in table 2.
Smith LA, Baraza W, Tiffin N et al. (2008) Endoscopic resection of adenoma-like mass in chronic ulcerative colitis using a combined endoscopic mucosal resection and cap assisted submucosal dissection technique. Inflammatory Bowel Diseases 14(10): 1380–6	Case series n = 67 Follow-up = 1.5 years	En bloc resection rate: 78% (52/67) with R0 resection rate in 94% (49/52) of these patients. Overall cure rate for ESD-assisted EMR was 98% (66/67) at median 19 months of follow-up. Bleeding complications in 10% (7/67). 2 perforations managed with endoclip.	Larger studies in table 2.
Tamegai Y, Saito Y, Masaki N et al. (2007) Endoscopic submucosal dissection: a safe technique for colorectal tumors. Endoscopy 39(5): 418–22	Case series n = 70 Follow-up = 12.2 months	En bloc resection rate was 98.6% with no recurrence at 12.2 months. 6.3% recurrence in the 32 treated with piecemeal ESD. 1 perforation successfully treated conservatively.	Larger studies with longer follow-up are included in table 2.
Tanaka S, Oka S, Kaneko I et al. (2007) Endoscopic submucosal dissection for colorectal neoplasia: possibility of standardization. Gastrointestinal Endoscopy 66(1): 100–7	Case series n = 70 lesions Follow-up = 614 days (~21 months)	En bloc resection rate: 80% (56/70) No recurrence or metastases observed in average follow-up of 614 days. 10% (7) perforation rate, 1.4% (1) postoperative haemorrhage	Larger studies in table 2.
Toyanaga T, Man I, Ivanov D et al. (2008) The results and limitations of endoscopic submucosal dissection for colorectal tumors. Acta Chirurgica Iugoslavica 55(3): 17–23	Case series n = 361 lesions Follow-up not reported	En-bloc resection rate: 95.2% (355/373) (the denominator includes 12 patients who were later determined to have deeply invasive cancer). Intraoperative perforation: 1.9% (6) Postoperative perforation: 0.3% (1)	Patients likely to be included in Toyanaga 2009 in table 2.

Yahagi N., Fujishiro M., and Omata M. (2004) Endoscopic submucosal dissection of colorectal lesion. Digestive Endoscopy 16 (Suppl 2): S178–S181	Case series n = 146 lesions	En bloc resection was attained in 92% (133). 87% (127) were considered to be completely resected by histological evaluation. No recurrence in en bloc group, 1 in piecemeal resection.	Larger studies with longer follow-up are included in table 2.
Yoshida N, Wakabayashi N, Kanemasa K et al (2009) Endoscopic submucosal dissection for colorectal tumors: Technical difficulties and rate of perforation. Endoscopy 41 (9) 758–761	Case series n = 100 (105 lesions)	En-bloc: 88.5% (93/105) Perforation in 10.4% (11/105) Recurrence not reported.	Larger studies in table 2.
Zhou P, Yao L, Qin X et al. (2009) Endoscopic submucosal dissection for locally recurrent colorectal lesions after previous endoscopic mucosal resection. Diseases of the Colon & Rectum 52(2): 305–10	Case series n = 73 (74 lesions)	En bloc resection 93.2% (69/74) 1 patient bled for 8 days; 8.1% (6/74) perforation rate, all recovered within several days of conservative treatment.	Larger studies in table 2.

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

Guidance	Recommendations
Interventional procedures	<p>Computed tomographic colonography (virtual colonoscopy). NICE interventional procedure 129 (2005)</p> <p>1.1 Current evidence on the safety and efficacy of computed tomographic colonography (virtual colonoscopy) appears adequate to support the use of this procedure provided that the normal arrangements are in place for consent, audit and clinical governance.</p>
Technology appraisals	<p>Laparoscopic surgery for the treatment of colorectal cancer. NICE technology appraisal 105 (2006)</p> <p>1.1 Laparoscopic (including laparoscopically assisted) resection is recommended as an alternative to open resection for individuals with colorectal cancer in whom both laparoscopic and open surgery are considered suitable.</p> <p>1.2 Laparoscopic colorectal surgery should be performed only by surgeons who have completed appropriate training in the technique and who perform this procedure often enough to maintain competence. The exact criteria to be used should be determined by the relevant national professional bodies. Cancer networks and constituent Trusts should ensure that any local laparoscopic colorectal surgical practice meets these criteria as part of their clinical governance arrangements.</p> <p>1.3 The decision about which of the procedures (open or laparoscopic) is undertaken should be made after informed discussion between the patient and the surgeon. In particular, they should consider:</p> <ul style="list-style-type: none"> • the suitability of the lesion for laparoscopic resection • the risks and benefits of the two procedures • the experience of the surgeon in both procedures. <p>Capecitabine and oxaliplatin in the adjuvant treatment of stage III (Dukes' C) colon cancer. NICE technology appraisal 100 (2006)</p> <p>1.1 The following are recommended as options for the adjuvant treatment of patients with stage III (Dukes' C) colon cancer following surgery for the condition:</p> <ul style="list-style-type: none"> • capecitabine as monotherapy • oxaliplatin in combination with 5-fluorouracil and folinic acid. <p>1.2 The choice of adjuvant treatment should be made jointly by the individual and the clinicians responsible for treatment. The</p>

	decision should be made after an informed discussion between the clinicians and the patient; this discussion should take into account contraindications and the side-effect profile of the agent(s) and the method of administration as well as the clinical condition and preferences of the individual.
--	---

Appendix C: Literature search for endoscopic submucosal dissection of lower gastrointestinal lesions

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	4/12/2009	Issue 4, 2009
Database of Abstracts of Reviews of Effects – DARE (CRD website)	4/12/2009	N/A
HTA database (CRD website)	4/12/2009	N/A
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	4/12/2009	Issue 3, 2009
MEDLINE (Ovid)	4/12/2009	1950 to July Week 3 2009
MEDLINE In-Process (Ovid)	4/12/2009	July 27, 2009
EMBASE (Ovid)	4/12/2009	1980 to 2009 Week 30
CINAHL (NLH Search 2.0 or EBSCOhost)	4/12/2009	N/A
BLIC (Dialog DataStar)	4/12/2009	N/A
Zetoc	4/12/2009	N/A

Websites searched on 4/12/2009

- 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	14 or 15
17	((colon* or rectum* or rectal* or colorectal* or anus* or anal* or bowel* or (large adj3 intestine*) or (lower adj3 gastrointestin*) or (taenia* adj3 coli*) or (appendix* adj3 epiploica*) or (lower adj3 intestin*) or villous*) adj3 (ulcer* or lesion* or adenoma* or polyp* or dysplas*)).tw.
18	Colonic Polyps/
19	Intestinal Polyps/
20	Adenoma, Villous/
21	Fissure in Ano/
22	Precancerous Conditions/
23	(precancer* or pre-cancer* or pre-malign* or premalign* or preneoplast* or pre-neoplastic*).tw.
24	((early or flat* or benign* or intramucosal*) adj3 (neoplasm* or cancer* or carcinoma* or adenocarcinom* or adenoma* or tumour* or tumor* or malignan*)).tw.
25	22 or 23 or 24