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
- Association of Cancer Physicians (Royal College of Physicians)
- Association of Endoscopic Surgeons of Great Britain and Ireland
- 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 dissect 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 and usually also with the administration of an opiate (general anaesthesia is sometimes required). 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 safety. Sometimes the colonoscope has a water-jet system to clean the area for increased visibility.

The submucosa is injected with fluid (usually sodium hyaluronate) which 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 direct vision, 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 haemostatis. Sometimes an endoclip is used to control bleeding and treat small perforations.

List of studies included in the overview

This overview is based on approximately 1895 patients from a systematic review of 14 studies (1314 patients), 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].

Case series not included in the meta-analysis reported en bloc resection rates of 95% (355/373)[2], 80% (133/166)[5], 79% (33/42)[6] and 89% (31/35)[7]. In the case series of 42 and 35, en bloc resections included complete margins (classified as R0) in 74% (31/42)[6] and 63% (22/35)[7] of patients, respectively.

Recurrence

A case series of 198 patients (200 lesions) reported that, of the 180 lesions followed up by colonoscopy, there was 1 case of local recurrence in a lesion treated by piecemeal resection (due to a failure of en bloc resection) at a median follow-up of 220 days[3].

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 months[4]. 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-up[6]. 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 ESD[4].

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]. Most were detected during the procedure and most were treated successfully with endoclip insertion.

A study reported a rate of 5% (27/528) perforations in patients treated with gastrointestinal tract ESD at one centre[8]. 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 endoclips in 1% (2/200) of lesions treated[4]. 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 procedure[10]. 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 28 July 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; LST-NG, laterally spreading tumour, non-granular; LST-G, laterally spreading tumour, granular; m, mucosal; R0, complete resection; R1, complete resection; Rx, margins not evaluable; sm, submucosal

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Puli (2009)[1]

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 criteria: completion of data and inclusion criteria since there was no control arm</td>
<td>Number of patients analysed: 1314
Completeness of resection
<table>
<tr><th>Study</th><th>Proportion of en bloc resection (95% CI)</th><th>Proportion of complete cure* (95% CI)</th></tr>
<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>
</table>
*Complete cure defined as en bloc plus histological disease-free margins
The pooled proportions were calculated with a random effects model.
Subgroup analysis
<table>
<tr><th>Study size (patients)</th><th>No. of studies</th><th>Proportion of en bloc resection (95% CI)</th><th>Proportion of complete cure (95% CI)</th></tr>
<tr><td><100</td><td>9</td><td>82.60 (66.45 –</td><td>71.23 (57.17 – 83.46)</td></tr>
</table>
</td>
<td>Not reported</td>
<td>Follow-up issues:
• No information on follow-up given for the studies.

Study design issues:
• 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.</td>
</tr>
</table>

Abbreviations used: CI, confidence interval; CT, computed topography; ESD, endoscopic submucosal dissection; LST-NG, laterally spreading tumour, non-granular; LST-G, laterally spreading tumour, granular; m, mucosal; R0, complete resection; R1, complete resection; Rx, margins not evaluable; sm, submucosal

Study details	Key efficacy findings				Key safety findings	Comments
Technique: ESD Follow-up: **not reported** Conflict of interest/source of funding: not reported			94.22)			**Study population issues**: • Study populations were not described. **Other issues** • This review included 3 studies which have been included in this table[3, 4, 7]. • No safety data were reported. • The study did not make clear if the patients being treated had prediagnosis before treatment.
	>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; LST-NG, laterally spreading tumour, non-granular; LST-G, laterally spreading tumour, granular; m, mucosal; R0, complete resection; R1, complete resection; Rx, margins not evaluable; sm, submucosal

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Toyanaga (2008)[2]

Case series
Japan, Serbia
Recruitment period: 2002–2007
Study population: colorectal lesions (118 adenoma, 177 mucosal cancer, 66 submucosal cancer)
n = 361 lesions (patient numbers not given)
Age: not reported
Sex: not reported
Patient selection criteria: lesions without metastases (without deep invasion , no lymph invasion); lesions >20 mm
Technique: ESD with diluted sodium hyaluronate injection and water-jet short needle knives

Follow-up: not reported

Conflict of interest/source of funding: not reported</td>
<td>Number of patients analysed: not stated (361 lesions)

Completeness of resection
Overall en bloc complete resection rate: 95.2% (355/373) (the denominator includes 12 patients who were later determined to have deeply invasive cancer).

En bloc complete resection was 98.3% (355/361).
en bloc

Additional outcomes
<table>
<tr><th></th><th>Median value</th></tr>
<tr><td>Tumour size</td><td>30 mm (range 6 – 158)</td></tr>
<tr><td>Specimen size</td><td>40 mm (16 – 165)</td></tr>
<tr><td>Procedure time</td><td>58 min (15 – 335)</td></tr>
</table>
</td>
<td>Complications
<table>
<tr><th></th><th>% of patients</th></tr>
<tr><td>Postoperative bleeding (no transfusion needed)</td><td>0.8% (3)</td></tr>
<tr><td>Intraoperative perforation</td><td>1.9% (6)*</td></tr>
<tr><td>Postoperative perforation</td><td>0.3% (1)**</td></tr>
</table>
Denominator not reported.
*5 cases treated conservatively (not further described) and 1 case treated surgically
**Treated surgically.</td>
<td>Follow-up issues:
This was not explicitly stated but the outcomes appear to relate to the immediate postoperative period.
Study design issues:
It is unclear if the resection rate includes the accuracy of margins.
Other issues
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).</td>
</tr>
</table>

Abbreviations used: CI, confidence interval; CT, computed topography; ESD, endoscopic submucosal dissection; LST-NG, laterally spreading tumour, non-granular; LST-G, laterally spreading tumour, granular; m, mucosal; R0, complete resection; R1, complete resection; Rx, margins not evaluable; sm, submucosal

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Saito (2007)[3]

Case series
Japan
Recruitment period: 2003–2006
Study population: Location: rectal (61) or colonic lesions (right colon: 97, left colon: 42); Histopathology: adenoma (51), intramucosal cancer (99); Appearance: 10 LST-NG, 7 LST-G, 12 depressed, 9 sessile, 9 recurrent (with ulcer scar)

n = 198 (200 lesions)
Mean age: 64
Sex: 58% male
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)
Technique: ESD with glycerol and sodium hyaluronate acid injection</td>
<td>Number of patients analysed: 198 (200 lesions)
Completeness of resection
En bloc resection was 84% (168/200).
Overall en bloc resection rate with tumour-free margins was 70% (140/200) en bloc

Local recurrence or residual tumour
Among those who were followed up by colonoscopy (90% [180/200] of lesions over a median of 220 days), there was 1 case of local recurrence in a lesion previously treated by piecemeal resection. There were no distance or lymph-node metastases.

Other
Mean tumour size: 35 mm
Mean resected specimen size: 28 mm
91% were >20 mm.
5% had scars from previous EMR.

NB: 28 of the treated lesions 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.

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’</td>
<td>Complications
<table><tr><th>Event</th><th>% of patients</th></tr><tr><td>Death</td><td>0</td></tr><tr><td>Postoperative bleeding</td><td>2% (4/200)*</td></tr><tr><td>Colonic-wall perforations</td><td>5% (10/200)**</td></tr></table>*1 within 24 hours, the others within 2 to 3 days; 3 were successfully controlled by endoscopic treatment with haemoclipping and/or electrocoagulation; 1 case needed observation for 1 day; no surgical intervention or blood transfusions required.
**All detected endoscopically during ESD; all were managed successfully with endoclips except for 1 requiring surgery

Perforation subanalysis
<table><tr><th colspan="2">Characteristics of the 10 perforations</th></tr><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 endoclip
1 surgery</td></tr></table></td>
<td>Follow-up issues:
Not reported (assumed to be postoperative; 90% (180/200) were followed up for 220 days).
Other issues:
This study was also included in the systematic review[1].
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 procedure was performed).
Study included a small proportion of patients with known relatively advanced local cancer in whom ESD was preferred to surgery because of balancing</td>
</tr>
</table>

Abbreviations used: CI, confidence interval; CT, computed topography; ESD, endoscopic submucosal dissection; LST-NG, laterally spreading tumour, non-granular; LST-G, laterally spreading tumour, granular; m, mucosal; R0, complete resection; R1, complete resection; Rx, margins not evaluable; sm, submucosal			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Follow-up: **overall follow-up not reported; however, 90% (180/200) of lesions were assessed at a median follow-up of 220 days (>7 months).** Conflict of interest/source of funding: "no commercial associations…that might be a conflict of interest".			operative risk against risk of incomplete resection.

Abbreviations used: CI, confidence interval; CT, computed topography; ESD, endoscopic submucosal dissection; LST-NG, laterally spreading tumour, non-granular; LST-G, laterally spreading tumour, granular; m, mucosal; R0, complete resection; R1, complete resection; Rx, margins not evaluable; sm, submucosal

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Fujishiro (2007)[4]

Case series
Japan
Recruitment period: 2000–2006
Study population: patients with preoperative diagnoses of mucosal or slight submucosal invasive (sm1) neoplasms (102 adenomas, 72 noninvasive carcinomas, 26 invasive carcinomas)
n = 186 (200 lesions)
Age: not reported
Sex: not reported
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
Patients with carcinoid tumours and invasive carcinomas treated with palliative fashion were excluded this analysis.
Technique: ESD with endoscope with water-jet system (no water-jet used</td>
<td>Number of patients analysed: 186 (200 lesions)

Completeness of resection
<table>
<tr><th></th><th>Percentage of patients</th></tr>
<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>
</table>
Additional treatment was required in 4 patients. Each had colorectal resection with lymphadenectomy because of tumour depth and/or vessel infiltration.
For those in whom an en bloc resection was not possible, piecemeal resection was performed.
Local recurrence (n = 111 tumours; 54 adenomas, 42 intramucosal carcinomas, 15 SM1 carcinomas)
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):
• 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.

Survival (n = 77 patients; 53 intramucosal carcinoma, 18 SM1 carcinoma, 6 SM2 or deeper carcinomas; 7 had suspected nodal metastasis)</td>
<td>Complications
All patients had minor bleeding during the procedure but haemostasis was achieved in each. There were no cases of massive haemorrhage
<table>
<tr><th>Event</th><th>% of patients</th></tr>
<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>
</table>
*Managed with conservative medical treatment after endoscopic closure of the perforation
**Patient also had diabetes mellitus, hypertension, post-sigmoidectomy and post-left nephrectomy and chronic renal failure with haemodialysis (unknown cause of perforation).
***Follow-up: same day as the procedure and 10 days after</td>
<td>Follow-up issues:
• Not all patients were followed up for recurrence (111 tumours were reported on for recurrence); only 77 patients followed up at mean 24 months.
Study design issues:
• The procedures were performed by 2 surgeons experienced in performing ESD for gastric tumours.

Study population issues:
• 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.

Other issues:
• This study was included in the systematic review above[1].
• 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)</td>
</tr>
</table>

Abbreviations used: CI, confidence interval; CT, computed topography; ESD, endoscopic submucosal dissection; LST-NG, laterally spreading tumour, non-granular; LST-G, laterally spreading tumour, granular; m, mucosal; R0, complete resection; R1, complete resection; Rx, margins not evaluable; sm, submucosal			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
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 Median follow-up: **24 months (for 77 patients)** Conflict of interest/source of funding: not reported	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. 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.		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.

Abbreviations used: CI, confidence interval; CT, computed topography; ESD, endoscopic submucosal dissection; LST-NG, laterally spreading tumour, non-granular; LST-G, laterally spreading tumour, granular; m, mucosal; R0, complete resection; R1, complete resection; Rx, margins not evaluable; sm, submucosal

Study details	Key efficacy findings	Key safety findings	Comments
Kita (2007)[5] **Case series** Japan Recruitment period: 1998–2005 Study population: patients with early stage neoplastic lesions of the colon n = **166** Age: not reported Sex: not reported Patient selection criteria: lesions >20 mm Technique: ESD with sodium hyaluronate injection (after saline injection) including indigo dye and epinephrine Follow-up: **not reported** Conflict of interest/source of funding: not reported	Number of patients analysed: **166** ***Completeness of resection*** 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) ***Other*** Mean procedure time was 102 minutes. Mean diameter of lesions was 33 mm. 109 lesions were granular and 46 were non-granular 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).	***Complications*** **Event** / **Patients** Bleeding requiring further endoscopic examination or clip placement — 3 Perforation* — 7 *This was treated endoscopically using clips in 5, laparoscopically in 1 and conservatively in 1.	**Follow-up issues**: • This was not reported (assumed to be postoperative outcomes). **Study design issues**: • It was not described how many surgeons performed the procedures. • It is unclear if the en bloc resection rates include accuracy of margins. **Study population issues**: • Types of lesions were not described in the population. **Other issues** • It was not clear from the study if the patients being treated had prediagnosis before treatment.

Abbreviations used: CI, confidence interval; CT, computed topography; ESD, endoscopic submucosal dissection; LST-NG, laterally spreading tumour, non-granular; LST-G, laterally spreading tumour, granular; m, mucosal; R0, complete resection; R1, complete resection; Rx, margins not evaluable; sm, submucosal

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Hurlstone (2007)[6]

Case series
UK
Recruitment period: 2004–2006
Study population: patients with diagnosis of Paris 0 – II adenomas or LSTs who presented to Royal Hallamshire Hospital in Sheffield
n = 42
Median age: 68
Sex: 64% male
Patient selection criteria: neoplastic or LST (G or NG) >20 mm, those with T2 N1 disease, evidence of metastases were excluded.
Technique: on-site staging followed by ESD with sodium hyaluronic + adrenaline + indigo carmine
Median follow-up:
6 months (36 patients)
Conflict of interest/source of funding: study was funded by The Smith and Nephew Research Foundation, Bardhan Research and Education</td>
<td>Number of patients analysed: 42
Completeness of resection
<table>
<tr><th></th><th>Percentage of patients</th></tr>
<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>
</table>
*9 were dissected piecemeal so were considered R1 or Rx by definition.

Mortality
30-day mortality: 0%

Recurrence
36 of the 42 patients were followed up (median 6 months).
• 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</td>
<td>Complications
<table>
<tr><th>Event</th><th>Patients</th></tr>
<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>
</table>
*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
**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.</td>
<td>Follow-up issues:
• 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.
Study design issues:
• This study was a prospective case series. It was performed to assess the technical feasibility of cap-assisted ESD.
Study population issues:
• Of 56 patients considered for ESD, 14 were excluded based on the exclusion criteria.
Other issues
• 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</td>
</tr>
</table>

Abbreviations used: CI, confidence interval; CT, computed topography; ESD, endoscopic submucosal dissection; LST-NG, laterally spreading tumour, non-granular; LST-G, laterally spreading tumour, granular; m, mucosal; R0, complete resection; R1, complete resection; Rx, margins not evaluable; sm, submucosal			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Trust Research Foundation, Butterfield 'Sasakawa' Foundation (UK), Mason Medical Research Foundation and the Peel Research Foundation.			diagnosis.

Abbreviations used: CI, confidence interval; CT, computed topography; ESD, endoscopic submucosal dissection; LST-NG, laterally spreading tumour, non-granular; LST-G, laterally spreading tumour, granular; m, mucosal; R0, complete resection; R1, complete resection; Rx, margins not evaluable; sm, submucosal

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Fujishiro (2006)[7]

Case series
Japan
Recruitment period: 2001–2005
Study population: patients with preoperative diagnosis of large intraepithelial rectal neoplasia with submucosal fibrosis, located on rectal folds, or > 2 cm
n = 35
Age: not reported
Sex: not reported

Technique: ESD + hyaluronic acid + saline or 10% glycerine + 5% fructose + saline; after 2004 the submucosal injection included epinephrine + indigo carmine
Mean follow-up:
36 months

Conflict of interest/source of funding: none declared</td>
<td>Number of patients analysed: 35

Completeness of resection

<table>
<tr><th></th><th>Upper rectum (n = 21)</th><th>Lower rectum (n = 14)</th><th>Whole rectum (n = 35)</th></tr>
<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>
</table>
*Extending to the lateral margins (there were none extending to the basal margins)

*The R0 resection rate was significantly lower in the lower rectum ($p < 0.05$).

For those in whom an en bloc resection was not possible, piecemeal resection was performed.

Recurrence

The study authors mention that 3 patients had ‘abdominal surgery’ during follow-up but no details about the reason are described.

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.

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.</td>
<td>Complications

Perforations which were successfully managed conservatively with endoclip after endoscopic closure occurred in 5.7% (2/35) of patients.
• 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.

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.</td>
<td>Follow-up issues:
• This study has the longest mean follow-up in all studies retrieved and this is why it was included in this table.
Study design issues:
• 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.
Study population issues:
• These patients may have been included in Fujishiro (2007)[4].
• It is not stated why 3 patients required abdominal surgery.
Other issues:
• This study was also included in the systematic review reported above[1].
• 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.</td>
</tr>
</table>

Abbreviations used: CI, confidence interval; CT, computed topography; ESD, endoscopic submucosal dissection; LST-NG, laterally spreading tumour, non-granular; LST-G, laterally spreading tumour, granular; m, mucosal; R0, complete resection; R1, complete resection; Rx, margins not evaluable; sm, submucosal			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
			• Prediagnosis was determined by chromoendoscopy with or without magnifying endoscopy.

Abbreviations used: CI, confidence interval; CT, computed topography; ESD, endoscopic submucosal dissection; LST-NG, laterally spreading tumour, non-granular; LST-G, laterally spreading tumour, granular; m, mucosal; R0, complete resection; R1, complete resection; Rx, margins not evaluable; sm, submucosal

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Fujishiro (2006)[8]

Case series
Japan
Recruitment period: 2000–2005
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).
n = 9 perforations
Of the 27 with perforations:
Mean age: 65
Sex: 85% male

Technique: ESD
Median follow-up: 36 months

Conflict of interest/source of funding: none</td>
<td colspan="2">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.

Occurrence of perforation
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).
<table>
<tr><th>Location</th><th>No. of perforations</th></tr>
<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>
</table>
(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.)

Description of perforations
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.
The patients were then treated conservatively or surgically. Those with perforations identified after the procedure were usually considered for surgical repair.

Recurrence
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).

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 treated by ESD. These</td>
<td>Study design issues:
• 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.
Study population issues:
• 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.
Other issues:
• 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.</td>
</tr>
</table>

Abbreviations used: CI, confidence interval; CT, computed topography; ESD, endoscopic submucosal dissection; LST-NG, laterally spreading tumour, non-granular; LST-G, laterally spreading tumour, granular; m, mucosal; R0, complete resection; R1, complete resection; Rx, margins not evaluable; sm, submucosal

Study details	Key efficacy findings	Key safety findings	Comments
	rates were reported by the chief of endoscopy at each centre.		

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; LST-NG, laterally spreading tumour, non-granular; LST-G, laterally spreading tumour, granular; m, mucosal; R0, complete resection; R1, complete resection; Rx, margins not evaluable; sm, submucosal

Study details	Key efficacy findings	Key safety findings	Comments
Park (2008)[10] **Case report** Korea Recruitment period: not reported Study population: 65-year old male with a LST at the caecal base n = **1** Technique: ESD with sodium hyaluronate injection Median follow-up: **postoperatively** Conflict of interest/source of funding: not reported	***Report of safety event:*** 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.		

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 tract[9].
- 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 months[7].
- 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 table[6].
- 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 (2007)[3] and the earlier patients treated in studies published by Fujishiro were injected with submucosal solutions including glycerol and fructose[4,7].
- 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 Advisers agree that it is a novel procedure of uncertain safety and efficacy. One 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 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 Adviser highlighted that there are a wide variety of knives with a variety of diathermy settings which can cause some confusion.
- One of the Advisers commented that the hospital where they work has been prospectively collecting data on the procedure.
- One 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 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 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.
- An 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. 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

3. 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

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

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
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. Gastrointestinal Endoscopy 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.
Hurlstone DP, Shorthouse AJ, Brown SR et al. (2008) Salvage endoscopic submucosal dissection for residual or local recurrent intraepithelial neoplasia in the colorectum: a prospective analysis. Colorectal Disease 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. Endoscopy 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.
Moon JH, Kim JH, Park CH et al. (2006) Endoscopic submucosal resection with double ligation technique for treatment of small rectal carcinoid tumors. Endoscopy 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. Digestive Diseases & Sciences 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. Endoscopy	Case series n = 35 Follow-up = 25.7 months	One-piece resection rate with tumour-free margins was achieved in all but 9 patients.	Larger studies in table 2.

39(5): 423–7		2.9% (1) perforation rate	
Repici A, Conio M, De Angelis C et al. (2007) Insulated-tip knife endoscopic mucosal resection of large colorectal polyps unsuitable for standard polypectomy. American Journal of Gastroenterology 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 cancer. Digestive Endoscopy OL 19; Suppl 1: S39	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.
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	Larger studies with longer follow-up are included in table 2.

		conservatively.	
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.
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.
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	**Computed tomographic colonography (virtual colonoscopy). NICE interventional procedure 129 (2005)** 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.
Technology appraisals	**Laparoscopic surgery for the treatment of colorectal cancer. NICE technology appraisal 105 (2006)** 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. 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. 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: • the suitability of the lesion for laparoscopic resection • the risks and benefits of the two procedures • the experience of the surgeon in both procedures. **Capecitabine and oxaliplatin in the adjuvant treatment of stage III (Dukes' C) colon cancer. NICE technology appraisal 100 (2006)** 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: • capecitabine as monotherapy • oxaliplatin in combination with 5-fluorouracil and folinic acid. 1.2 The choice of adjuvant treatment should be made jointly by the individual and the clinicians responsible for treatment. The

	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	No. retrieved
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	28 July 2009	Issue 3, 2009	9
Database of Abstracts of Reviews of Effects – DARE (CRD website)	28 July 2009	N/A	1
HTA database (CRD website)	28 July 2009	N/A	0
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	28 July 2009	Issue 3, 2009	14
MEDLINE (Ovid)	28 July 2009	1950 to July Week 3 2009	350
MEDLINE In-Process (Ovid)	28 July 2009	July 27, 2009	38
EMBASE (Ovid)	28 July 2009	1980 to 2009 Week 30	298
CINAHL (NLH Search 2.0 or EBSCOhost)	28 July 2009	N/A	23
BLIC (Dialog DataStar)	28 July 2009	N/A	39

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