# NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

## INTERVENTIONAL PROCEDURES PROGRAMME

## Interventional procedure overview of endoscopic submucosal dissection of oesophageal dysplasia and neoplasia

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

## Introduction

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

## Date prepared

This overview was prepared in February 2010.

## Procedure name

- Endoscopic submucosal dissection of oesophageal dysplasia and neoplasia

## Specialty societies

- British Society of Gastroenterology
- Association of Upper Gastrointestinal Surgeons for Great Britain and Ireland

# Description

## *Indications and current treatment*

*Dysplastic (pre-malignant) and neoplastic (malignant) oesophageal lesions*

Such lesions may arise as part of disease processes relating to two different malignancies: oesophageal squamous cell carcinoma (OSCC) and oesophageal adenocarcinoma (OAC).

*Aspects of descriptive epidemiology:*

OSCC used to be the predominant type of oesophageal cancer in the UK, however in recent decades its incidence has been declining. In contrast, over the same period there has been a continuous rise in the incidence of OAC, most likely reflecting similar trends in increasing prevalence of Barrett's oesophagus (a pre-malignant condition for OAC). Currently, about two thirds of all oesophageal cancers in the UK are adenocarcinomas, with squamous carcinomas making up the other third. Although similar epidemiological trends were observed in some other countries (such as the USA), in other countries (such as Japan) OSCC remains the predominant oesophageal cancer type.

*Mode of presentation:*

- *OSCC:* In the UK, patients with OSCC typically present at a symptomatic stage (e.g. with dysphagia). There is also little experience in treating squamous dysplasia.

- *OAC and high-grade dysplasia (HGD):* In the UK, although most patients present at symptomatic stage, some patients (typically with a previous diagnosis of Barrett's oesophagus) are identified at an early stage (with intramucosal cancer) or with HGD.

In other countries (e.g. Japan) the proportion of patients with either OSCC or OAC who are diagnosed with early stage disease is thought to be much higher than that in the UK.

*Current management*:

About a quarter of all patients with oesophageal cancer (of whichever type) present with operable disease and for those patients, oesophagectomy offers the possibility of cure. Chemotherapy and radiotherapy may also be used, depending on tumour type and stage, either with a palliative or curative intent.

Patients with oesophageal HGD may be managed either by oesophagectomy or frequent surveillance with subsequent oesophagectomy if HGD persists or progresses. However, during the last decade, a series of endoscopic treatments have also been developed, including endoscopic mucosal resection (EMR) and ablative modalities (such as radiofrequency ablation).

EMR involves injection of a solution into the submucosal layer underneath the lesion in order to raise it and ease its removal using a snare.

*Lesion stage and morphology classifications*

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

- m1, intraepithelial carcinoma
- m2, microinvasive carcinoma (invasion through the basement membrane)
- m3, intramucosal carcinoma (invasion to the muscularis mucosae)
- sm1, superficial invasion in the submucosa (less than 200 micrometres below the muscularis mucosae)
- sm2 or sm3, middle invasion in the submucosa (more than 200 micrometres below the muscularis mucosae).

For lesion morphology, a commonly used classification scheme is the Paris system. Polypoid lesions (protruding into the lumen) are classified as 0–I (Ip, Ips or Is depending on whether or not they are pedunculated, subpedunculated or sessile). Non-polypoid lesions are classified as 0–IIa if they are slightly elevated, 0–IIb if they are flat without elevation or depression, and 0–IIc if they have a central mucosal depression. Combination categories also exist such as 0–IIc and IIa for lesions that have mucosal depression with an elevated edge. Ulcerated lesions are characterised as 0–III.

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) and 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 usually undergo endoscopy and biopsy as well as imaging investigations as part of the diagnostic work-up. The procedure can be performed with the patient under sedation or under general anaesthesia with endoscopic visualisation.

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. Small quantities of a pigment dye may be included in the submucosal

injection to help delineate the lesion, and adrenaline may be included to reduce the risk of bleeding.

An initial circumferential mucosal incision is made with the electrocautery knife around the lesion. Submucosal resection is then performed under direct vision, parallel to the muscle layer, and then removed. A transparent hood may be used to retract the already dissected part of the lesion out of the field of view. Thermocoagulation is used to achieve haemostasis. Sometimes an endoscopic clip is used to control bleeding and treat small perforations.

Postoperatively, patients may drink water and a solid diet is gradually introduced over the following week.

# Literature review

## *Rapid review of literature*

The medical literature was searched to identify studies and reviews relevant to endoscopic submucosal dissection of oesophageal dysplasia and neoplasia. Searches were conducted of the following databases, covering the period from their commencement to 19 May 2010: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

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

**Table 1 Inclusion criteria for identification of relevant studies**

| Characteristic | Criteria |
|---|---|
| Publication type | Clinical studies were included. Emphasis was placed on identifying good quality studies.<br>Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study.<br>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 oesophageal dysplasia and neoplasia. |
| Intervention/test | Endoscopic submucosal dissection. |
| Outcome | Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy. |
| Language | Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base. |

## *List of studies included in the overview*

This overview is based on approximately 578 patients from 2 comparative case series, 7 case series and 1 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.

## Table 2 Summary of key efficacy and safety findings on endoscopic submucosal dissection of oesophageal dysplasia and neoplasia

| Abbreviations used: CI, confidence interval; CT, computerised tomography; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; HGIN, high-grade intraepithelial neoplasm; IV, intravenous; M, mucosal; OR, odds ratio; PPI, proton pump inhibitor; OSCC, oesophageal squamous cell carcinoma; SM, submucosal | | | |
|---|---|---|---|
| **Study details** | **Key efficacy findings** | **Key safety findings** | **Comments** |

Abbreviations used: CI, confidence interval; CT, computerised tomography; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; HGIN, high-grade intraepithelial neoplasm; IV, intravenous; M, mucosal; OR, odds ratio; PPI, proton pump inhibitor; OSCC, oesophageal squamous cell carcinoma; SM, submucosal

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Ishihara R (2008)[1]<br>Comparative case series<br>Japan<br>Recruitment period: 2002–2007<br>Study population: histologically proven early oesophageal cancer (mainly OSCC, see below) with lesions ≤20 mm<br>n = 136 (171 lesions): 31 lesions ESD, 68 lesions EMR with transparent cap, 72 lesions 2-channel EMR<br>Mean age (years): 64 (ESD), 65 (EMR + cap), 61 (2-channel EMR)<br>Sex: 86% (ESD), 86% (EMR + cap), 88% (2-channel EMR) male<br>Location: 35 upper 1/3, 76 middle 1/3, 60 lower 1/3<br>Histopathology: 168 OSCC, 3 adenocarcinoma<br>Depth: 128 m1, 36 m2, 15 m3, 2 sm1<br>Patient selection criteria: tumour invasion depth m1 – sm1 without lymphovascular involvement, no additional treatment immediately after the procedure, no prior chemotherapy or radiation therapy, no multiple lesions in nearby mucosa<br><br>Technique: both ESD and EMR under IV sedation with a saline injection (including 10% glycerin and epinephrine) and then saline; EMR first performed with a 2-channel endoscope and then with a transparent cap ; chromoendoscopy, then iodine injection to mark the lesion<br><br>Follow-up: not reported<br>Conflict of interest/source of funding: none</td>
<td>Number of patients analysed: 136 (171 lesions): 31 lesions ESD, 68 lesions EMR with transparent cap, 72 lesions 2-channel EMR<br><br>Completeness of resection Curative rate defined as en-bloc with tumour-invasion depth of m1 to sm1 with no lymphovascular involvement and tumour-free margins (piece-meal not included).
<table>
<tr><th>Size</th><th>ESD</th><th>EMR + cap</th><th>2-channel EMR</th></tr>
<tr><td colspan="4">En-bloc rate</td></tr>
<tr><td><5 mm</td><td>n/a</td><td>n/a</td><td>100 (4/4)</td></tr>
<tr><td>5-<10mm</td><td>100 (3/3)</td><td>100 (14/14)</td><td>80 (12/15)</td></tr>
<tr><td>10-<15 mm</td><td>100 (7/7)</td><td>100 (23/23)</td><td>87 (26/30)</td></tr>
<tr><td>≥15 mm</td><td>100 (21/21)[a]</td><td>71 (22/31)</td><td>39 (9/23)</td></tr>
<tr><td>Total</td><td>100 (31/31)[b]</td><td>87 (59/68)</td><td>71 (51/72)</td></tr>
<tr><td colspan="4">Curative rate</td></tr>
<tr><td><5 mm</td><td>n/a</td><td>n/a</td><td>100 (4/4)</td></tr>
<tr><td>5-<10mm</td><td>100 (3/3)</td><td>93 (13/14)[b]</td><td>40 (6/15)</td></tr>
<tr><td>10-<15 mm</td><td>100 (7/7)[b]</td><td>83 (19/23)[b]</td><td>50 (15/30)</td></tr>
<tr><td>≥15 mm</td><td>95 (20/21)[b]</td><td>52 (16/31)[b]</td><td>35 (8/23)</td></tr>
<tr><td>Total</td><td>97 (30/31)[a]</td><td>71 (48/68)[b]</td><td>46 (33/72)</td></tr>
</table>
[a] p < 0.05 between ESD and both EMR types</td>
<td>Complications
<table>
<tr><th></th><th>No. of occurences</th><th>Group</th></tr>
<tr><td>Perforation with mediastinal emphysema*</td><td>1*</td><td>ESD</td></tr>
<tr><td>Postoperative bleeding</td><td>1</td><td>EMR + cap</td></tr>
<tr><td>Postoperative stricture**</td><td>3</td><td>EMR + cap</td></tr>
</table>
*this occurred during the procedure and was successfully treated with antibiotics (there was not mention of use of an endoscopic clip)<br>**successfully treated by endoscopic balloon dilation</td>
<td>Follow-up issues:<ul><li>Iodine staining with endoscopy 3, 9 months and annually; CT at least once a year to detect lymph node or distance metastases.</li><li>Local recurrence was diagnosed with iodine scar was identified adjacent to scar and biopsy was taken.</li></ul>Study design issues:<ul><li>Retrospective, single centre.</li><li>Patients reported in this study were taken from a database of 241 patients (341 lesions) that fit the inclusion criteria. It was not reported how these patients were selected for endoscopic resection over surgery.</li><li>The older version of EMR with a 2-channel endoscope was mostly used from 2002 to Aug 2005; EMR with the use of a transparent cap was used from this period onwards. ESD was mainly used from</li></ul></td>
</tr>
</table>

| Abbreviations used: CI, confidence interval; CT, computerised tomography; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; HGIN, high-grade intraepithelial neoplasm; IV, intravenous; M, mucosal; OR, odds ratio; PPI, proton pump inhibitor; OSCC, oesophageal squamous cell carcinoma; SM, submucosal | | | |
|---|---|---|---|
| **Study details** | **Key efficacy findings** | **Key safety findings** | **Comments** |
| | [b] $p < 0.05$ with 2-channel EMR group<br>[c] $p < 0.01$ or 0.05 from 2-channel EMR group<br><br>Patients with submucosal invasion deeper than 200µm and or lymphovascular involvement on histological evaluation were treated with surgery or 'chemoradiation'.<br><br>***Local recurrence***<br>There were 2 local recurrences in the 2-channel EMR group which were successfully treated with additional endoscopic resection (one EMR with cap and one 2-channel EMR). There were no recurrences in the ESD and EMR + cap groups. | | May 2004 onwards.<br>**Study population issues**:<br>• The only significant difference between groups was the size of the tumour (ESD was larger).<br>• The actual number of patients treated per group was given in a table but it totaled 148. It was uncertain why there was a discrepancy of 12 patients.<br>**Other issues**<br>• All patients were confirmed histologically as having OSCC (predominantly) or adenocarcinoma (3 patients only); chromoendoscopy was used to evaluate the spread of the lesion. |

Abbreviations used: CI, confidence interval; CT, computerised tomography; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; HGIN, high-grade intraepithelial neoplasm; IV, intravenous; M, mucosal; OR, odds ratio; PPI, proton pump inhibitor; OSCC, oesophageal squamous cell carcinoma; SM, submucosal

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Ishihara R (2008)[2]<br><br>Comparative case series<br>Japan<br>Recruitment period: 1994–2006<br>Study population: patients with histologically proven OSCC lesions ≤20 mm<br>n = 77 (85 lesions): 27 (33 lesions) ESD vs 50 (52 lesions) EMR<br>Mean age: 65 years<br>Sex: 80% male<br>Location: cervical oesophagus (1), upper 1/3 (8), middle 1/3 (46), lower 1/3 (23)<br>Depth: m1 (40), m2 (17), m3 (16), sm1 (5)<br>Size: between 20 and 30 mm (46), > 30 mm (32)<br><br>Patient selection criteria: tumour invasion depth m1 to sm1 without lymphovascular involvement, no additional treatment immediately after the procedure, tumour lesion <50 mm (unless requested by the patient), with follow-up longer than 1 year<br><br>Technique: ESD and EMR (with saline) under IV sedation with iodine staining before the procedure.<br><br>Median follow-up: 38 months (minimum 1 year)<br><br>Conflict of interest/source of funding: none</td>
<td>Number of patients analysed: 70 (78 lesions): 26 (32 lesions) ESD vs 44 (46 lesions) EMR<br><br>Completeness of resection<br><table><tr><th></th><th>En-bloc resection rate</th></tr><tr><td>ESD</td><td>90.6% (29/32)</td></tr><tr><td>EMR</td><td>10.9% (5/46)</td></tr></table><br>Local recurrence<br><table><tr><th></th><th>No. median follow-up 32 months (%)</th></tr><tr><td>ESD</td><td>1 (3.8%)</td></tr><tr><td>EMR</td><td>11 (25%)</td></tr><tr><td>Total</td><td>12 (15.4% )</td></tr></table>(time of detection not reported)<br>All were treated by piecemeal resection and all were superficial cancer. Patients treated with more multi-piece resection and treated by EMR had significantly more recurrences (no significance level reported) but there was no association between age, sex, coexistence of head and neck cancer, and tumour size or location.<br><br>All patients with recurrence had repeat EMR or endoscopic coagulation therapy.<br>Remission was achieved in 10 patients (4 had 1 additional procedure – endoscopic resection or coagulation – and 6 had 2 additional procedures).<br>One patient had another local recurrence</td>
<td>Complications<br><br>Postoperative stricture occurred in 24% (17/70) of patients. Each were successfully treated with endoscopic balloon dilation (difference in rate of stricture between EMR and ESD was not given; time of occurrence not reported).<br><br>Mediastinal emphysema occurred in 2 patients (7.7%) after ESD which was later determined on radiography to be because of microperforation or air passage through a gap of muscle fiber. Neither had respiratory symptoms and both recovered within 3 days with antibiotic administration (there was not mention of use of an endoscopic clip).</td>
<td>Follow-up issues:<ul><li>In ESD group 1 patient lost to follow-up; in EMR group, 4 lost to follow-up and 2 died of other diseases within one year.</li><li>3, 9 months and annually, iodine staining with endoscopy; CT at least once a year to detect lymph node or distance metastases.</li><li>Local recurrence was diagnosed with iodine scar was identified adjacent to scar and biopsy was taken.</li></ul>Study design issues:<ul><li>Retrospective study selected from 226 consecutive patients (335 lesions) which had large tumours (≤ 20 mm) and who had at least 1 year of follow-up). It was not reported how these patients were selected for endoscopic resection over surgery.</li></ul>Study population</td>
</tr>
</table>

| Abbreviations used: CI, confidence interval; CT, computerised tomography; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; HGIN, high-grade intraepithelial neoplasm; IV, intravenous; M, mucosal; OR, odds ratio; PPI, proton pump inhibitor; OSCC, oesophageal squamous cell carcinoma; SM, submucosal | | | |
|---|---|---|---|
| **Study details** | **Key efficacy findings** | **Key safety findings** | **Comments** |
| | after additional endoscopic resection and 'chemoradiation' therapy.<br>Another patient chose surgery for subsequent treatment.<br>At median follow-up 38 months after the last therapy, 75% (9/12) were alive and without further recurrence (the other 3 died of other diseases without further occurrence). | | **issues**:<br>• Differences between patients treated by EMR and ESD not reported.<br>**Other issues**<br>• All patients were confirmed histologically as OSCC. |

Abbreviations used: CI, confidence interval; CT, computerised tomography; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; HGIN, high-grade intraepithelial neoplasm; IV, intravenous; M, mucosal; OR, odds ratio; PPI, proton pump inhibitor; OSCC, oesophageal squamous cell carcinoma; SM, submucosal

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Ono S (2009)[3]<br><br>Case series<br>Japan<br>Recruitment period: 2002–2008<br>Study population: superficial OSCC or high-grade squamous dysplasia<br>n = 84 (107 lesions)<br>Age: not reported<br>Sex: not reported<br>Location: 7 upper, 59 middle, 31 lower, 10 abdominal oesophagus<br>Histopathology/depth: 57 high-grade dysplasia (referred to as ‘HGIN’ in the source), 20 m2, 16 m3, 5 sm1, 9 sm2<br>Mean size: 22.9 mm<br>Exclusion criteria: adenocarcinoma or other minor histopathological types<br><br>Technique: ESD with conscious sedation and local anaesthesia or, if inappropriate (upper thoracic lesions or predicted operating time >2 hours), general anaesthesia<br><br>Median follow-up: 632 days (approximately 21 months; 56 for >1 year)<br><br>Conflict of interest/source of funding: none</td>
<td>Number of patients analysed: 84 (107 lesions)<br>Completeness of resection
<table>
<tr><th></th><th>% of lesions (no.)</th></tr>
<tr><td>En-bloc resection</td><td>100 (107/107)</td></tr>
<tr><td>R0 resection</td><td>87.9 (94/107)</td></tr>
<tr><td>R1 (lateral) resection</td><td>4.7 (5/107)</td></tr>
<tr><td>R1 (basal) resection</td><td>1.9 (2/107)</td></tr>
<tr><td>Rx (lateral) resection</td><td>5.6 (6/107)</td></tr>
<tr><td>Rx (basal) resection</td><td>0</td></tr>
</table>
17.9% (15/84) of patients had possible node-positive tumours so underwent further treatments (5 ‘chemoradiation’, 1 radiation, 9surgery)<br>2.4% (2/84) of additional patients with submucosal OSCC also had possible node-positive tumours chose not to have additional therapy. None had recurrence at 22 and 26 month follow-up (both had CT every 6 months, 1 had endoscopy every 2 weeks to resolve stricture and then every 2months; 1 had endoscopy and CT every 6months<br><br>Local recurrence<br>There was 1 local recurrence in a patient with a previously diagnosed lesion as high grade dysplasia (‘HGIN’) with Rx (lateral) resection. This occurred at 6months and was successfully treated with another ESD session.</td>
<td>Complications
<table>
<tr><th></th><th>% of patients (no.)</th></tr>
<tr><td>Perforation with mediastinal emphysema*</td><td>4.8 (4)</td></tr>
<tr><td>Benign stricture with dysphagia**</td><td>17.9 (15)</td></tr>
</table>
* All were detected during the procedure by endoscopy and immediately treated successfully with endoscopic clips; all had IV antibiotics and not allowed to eat or drink for several days (the study reported that this was 4% of patients).<br>** These were managed successfully with balloon dilation; 93% (14/15) patients had lesion greater than half of the luminal circumference; 10 had greater than three quarters of the circumference.<br>Minor bleeding was encountered in each procedure but none required transfusion or additional endoscopy for haemostasis.</td>
<td>Follow-up issues:<br>• Follow-up endoscopy with iodine staining after 2 months, endoscopy at 6 and 12 months, and if postoperative diagnosis was required, distant and lymph node metastases were evaluated by CT.<br><br>Study design issues:<br>• Retrospective, 1 centre<br>• It was not reported how these patients were selected for endoscopic resection over surgery.<br><br>Study population issues:<br>• 15 patients with node-positive tumours had additional treatments: (all had histopathological diagnosis of invasive OSCC deeper than lamina propria mucosae or with vessel infiltration were recommended to have</td>
</tr>
</table>

| Abbreviations used: CI, confidence interval; CT, computerised tomography; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; HGIN, high-grade intraepithelial neoplasm; IV, intravenous; M, mucosal; OR, odds ratio; PPI, proton pump inhibitor; OSCC, oesophageal squamous cell carcinoma; SM, submucosal | | | |
|---|---|---|---|
| **Study details** | **Key efficacy findings** | **Key safety findings** | **Comments** |
| | Of 56 patients followed up for >1 year, 11 (20%) had more than 1 ESD session for neoplasms believed to be synchronous (i.e. being present at the same time as the 'index' tumour).<br>2 had a second ESD for neoplasia believed to be metachronous (i.e. diagnosed as new neoplasms after the index tumour was diagnosed) at 13 and 17 months follow-up<br><br>***Distant metastases***<br>In 2 patients who presented with m3 carcinoma, distant metastases occurred at 8- and 18-month follow-up. One had presented with vessel infiltration and the other did not (no other details provided, such as location of metastases).<br><br>***Survival***<br>18% (10) patients died in the follow-up period: 3 were due to oesophageal cancer and 10 from other diseases (not specified; denominator not given).<br>5-year overall survival rates were 95% in those with high-grade dysplasia ('HGIN') or m2 and 100% in those with m3 or sm.<br>5-year cause-specific survival rates: 56% in those with high-grade dysplasia or m2 and 85% in those with m3 or sm.<br>(rates were significantly higher for those with m3 or sm; $p \leq 0.05$) | | additional treatments.<br><br>**Other issues**:<br>• Prediagnosis was completed with endoscopic biopsy and preoperative diagnosis of possible high grade dysplasia ('HGIN') or intramucosal invasive OSCC with chromoendoscopy with iodine staining, narrow-band imaging and occasionally with ultrasound for lesions likely to have invaded the submucosa. |

Abbreviations used: CI, confidence interval; CT, computerised tomography; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; HGIN, high-grade intraepithelial neoplasm; IV, intravenous; M, mucosal; OR, odds ratio; PPI, proton pump inhibitor; OSCC, oesophageal squamous cell carcinoma; SM, submucosal

| Study details | Key efficacy findings | Key safety findings | Comments |
|---|---|---|---|
| Oyama T (2005)[4]<br><br>**Case series**<br>Japan<br>Recruitment period: 2000–2004<br>Study population: superficial OSCC<br>n = **102 cases** (not clear if number of patients or lesions)<br>Age: not reported<br>Sex: not reported<br>Mean size of lesion: 32 mm<br>Mean size of cancer: 28 mm<br><br>Patient selection criteria: not reported<br><br>Technique: ESD with hook knife<br><br>Mean follow-up: **21 months**<br><br>Conflict of interest/source of funding: not reported (but authors claim to be developers of the technique) | Number of patients analysed: **102 cases** (not clear if number of patients or lesions)<br><br>***Completeness of resection***<br>En-bloc resection rate: 93% (95/102)<br>(the study appears to have reported the percentage of en-bloc resection incorrectly so this has been corrected by the analyst)<br><br>***Local recurrence***<br>0% (0/102) | ***Complications***<br>5.9% (6/102) of cases had mediastinal emphysema treated with 2 days of IV antibiotics and fasting with IV infusion (time of occurrence not reported)<br>6.9% (7/102) of cases had stenosis requiring balloon dilatation (mucosa defect was greater than or equal to four fifths of the circumference in these cases) | **Follow-up issues**:<br>• How patients were followed up was not described.<br>**Study design issues**:<br>• It is unclear if the resection rate includes the accuracy of margins.<br>• It was not reported how these patients were selected for endoscopic resection over surgery.<br>**Other issues**:<br>• Despite reporting mediastinal emphysema in 6 patients, the authors also stated in the paper that there were no perforations.<br>• The authors state that they have developed the technique using a hook knife in order to resect lesions en-bloc to prevent local recurrence.<br>• The study did not make clear if the patients being treated had diagnostic confirmation before treatment. |

Abbreviations used: CI, confidence interval; CT, computerised tomography; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; HGIN, high-grade intraepithelial neoplasm; IV, intravenous; M, mucosal; OR, odds ratio; PPI, proton pump inhibitor; OSCC, oesophageal squamous cell carcinoma; SM, submucosal

| Study details | Key efficacy findings | Key safety findings | Comments |
|---|---|---|---|
| Ono S (2009)[5]<br><br>**Case series**<br>Japan<br>Recruitment period: 2002–2008<br>Study population: patients with high grade dysplasia (referred to as 'HGIN') or m2 OSCC<br>n = **65** (11 with stricture, 54 without)<br>Mean age: 67.8 years (with stricture), 67.5 years (without stricture)<br>Sex: 86% male<br>Location: upper thoracic (5), middle thoracic (38), lower thoracic (18), abdominal (4)<br>Macroscopic type (Paris classification): IIa (4), IIb (15), IIc (41), combined (5)<br>Depth: high grade dysplasia ('HGIN') (43), m2 (22)<br><br>Patient selection criteria: see 'other issues' section of comments.<br><br>Technique: ESD<br><br>Follow-up: **not reported**<br><br>Conflict of interest/source of funding: none | No efficacy reported. | Number of patients analysed: **65** (11 with stricture, 54 without)<br>**Rate of stricture:** 16.9% (11/65)<br>The 11 patients were treated with between 1 and 19 sessions of balloon dilatation over a period of 0 to 47.3 months. Four required less than 5 dilatations and 4 required more than 15. The period between dilatations was as large as 12 months.<br><br>Univariate analysis showed that the patients who developed stricture had significantly longer circumferential extent of the lesion, histologic depth, procedure time and both longitudinal diameter and circumferential diameter ($p < 0.0001$, $p = 0.0002$, $p = 0.0069$, $p = 0.0062$ and $p = 0.002$, respectively).<br><br>Multivariate analysis of these 5 variables revealed two risk factors associated with a high rate of postoperative stricture:<br>1. lesion extending to more than ¾ of the circumferential area (OR 44.2, 95% CI 4.4 to 443.6, $p = 0.0002$)<br>2. histological depth to m2 (OR 14.2, 95% CI 2.7 to 74.2, $p = 0.0002$). | **Follow-up issues**:<br>• Follow-up endoscopy with iodine staining at second month.<br>**Study design issues**:<br>• Retrospective study.<br>• It was not reported how these patients were selected for endoscopic resection over surgery.<br>• This study includes a subgroup of 116 patients treated by ESD. This study is likely to include patients reported in Ono 2009[3].<br>• The intention of this study is to investigate predictors of postoperative stricture.<br>**Other issues**:<br>• All lesions preoperatively proven or suspicious for OSCC by endoscopic biopsy and had preoperative diagnosis of possible high grade dysplasia or intramucosal invasive carcinoma by chromoendoscopy with iodine and narrow |

| Abbreviations used: CI, confidence interval; CT, computerised tomography; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; HGIN, high-grade intraepithelial neoplasm; IV, intravenous; M, mucosal; OR, odds ratio; PPI, proton pump inhibitor; OSCC, oesophageal squamous cell carcinoma; SM, submucosal | | | |
|---|---|---|---|
| **Study details** | **Key efficacy findings** | **Key safety findings** | **Comments** |
| | | | band imaging. |

Abbreviations used: CI, confidence interval; CT, computerised tomography; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; HGIN, high-grade intraepithelial neoplasm; IV, intravenous; M, mucosal; OR, odds ratio; PPI, proton pump inhibitor; OSCC, oesophageal squamous cell carcinoma; 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 M (2006)[9]<br><br>Case series<br>Japan<br>Recruitment period: 2002–2005<br>Study population: patients with superficial oesophageal squamous cell neoplasm<br>n = 43 (58 lesions)<br><br>Mean age: not reported<br>Sex: not reported<br>Location: upper thoracic (7), middle thoracic (29), lower thoracic (17), abdominal oesophagus (5)<br>Macroscopic type (Paris classification): IIa (2), IIb (20), IIc (35), IIc+IIa (1)<br>Depth/histopathology: 18 high-grade dysplasia, 24 m1, 8 m2, 11 m3, 4 sm1, 3 sm2 (40 lesions [31 patients] were considered to be node-negative tumours on histopathologic evaluation)<br>Mean lesion size: 24 mm<br><br>Patient selection criteria: high-grade intraepithelial neoplasia (high-grade dysplasia and noninvasive carcinoma) or intramucosal invasive carcinoma<br><br>Technique: ESD with hyaluronic acid preparation and normal saline or glycerin with fructose and saline<br><br>Follow-up = 17 months<br><br>Conflict of interest/source of funding: not reported</td>
<td>Number of patients analysed: 43<br><br>Completeness of resection<br><table><tr><th></th><th>% of lesions (no.)</th></tr><tr><td>En-bloc resection</td><td>100 (58/58)</td></tr><tr><td>R0 resection</td><td>77.6 (45/58)</td></tr><tr><td>R1 (lateral) resection</td><td>8.6 (5/58)</td></tr><tr><td>R1 (basal) resection</td><td>3.4 (2/58)</td></tr><tr><td>Rx (lateral) resection</td><td>10.3 (6/58)</td></tr><tr><td>Rx (basal) resection</td><td>0</td></tr></table><br>Local recurrence<br><u>Lesions preoperatively assessed as node-negative</u><br>Of the 40 lesions (31 patients) determined to have node negative tumours before the procedure, 22 (55%) were successfully followed-up endoscopically for more than 6 months. Only one patient (4.5%, 1/22) who had an Rx (lateral) resection had local recurrence of noninvasive carcinoma 6 months after ESD (during mean follow-up of 17 months). This was completely resected by another ESD with no further local recurrence in an additional 12 months of follow-up.<br>No lymph node metastases were observed.<br><u>Lesions preoperatively assessed to have high risk of modal metastases</u><br>Of the additional 18 lesions (16 patients) which were determined preoperatively to have high risk of nodal metastases, 5</td>
<td>Complications<br><table><tr><th></th><th>% of lesions (no.)</th></tr><tr><td>Perforation (< 4mm) with pneumomediastinum *</td><td>6.9 (4/58)</td></tr><tr><td>Oesophageal stricture with dysphagia**</td><td>15.5 (9/58)</td></tr></table>* time of occurrence not reported; diagnosed on endoscopy and successfully treated with endoscopic clipping and all cases of pneumomediastinum disappeared spontaneously within a week (confirmed by chest x-ray). All occurred before 2003 (when few patients had undergone the procedure).<br>** time of occurrence not reported; successfully treated with balloon dilation (repeated every 1-2 weeks after dysphagia was recognized); in 7 of these occurrences, lesions covered more than three quarters of the circumference of the oesophagus.<br><br>All dissections had minor bleeding which was successfully controlled with thermocoagulation without the use of clips.<br>No massive haemorrhage or blood transfusion was required.</td>
<td>Follow-up issues:<br>• At 2, 6 and 12 months, follow-up endoscopy was performed followed by annual endoscopic examinations. CT and endoscopic ultrasonography was used indefinitely to exclude distant or lymph node metastases.<br>• 18 lesions (of the 40 lesions) were excluded from follow-up: 4 had concurrent lesions requiring additional treatment, 8 were followed up at another hospital and 6 had less than 6 months of follow-up.<br>Study design issues:<br>• It appears that patients were given an option between ESD, EMR, ablation therapy, surgery, and radiation therapy (with or without chemotherapy).<br><br>Other issues<br>• Prediagnosis confirmed with</td>
</tr>
</table>

Abbreviations used: CI, confidence interval; CT, computerised tomography; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; HGIN, high-grade intraepithelial neoplasm; IV, intravenous; M, mucosal; OR, odds ratio; PPI, proton pump inhibitor; OSCC, oesophageal squamous cell carcinoma; SM, submucosal

| Study details | Key efficacy findings | Key safety findings | Comments |
|---|---|---|---|
| | patients (6 lesions) decided to be closely followed up without additional treatment (all had intramucosal invasive carcinoma into the muscularis mucosae [m3] and 1 had lymphatic vessel infiltration).<br><br>During a mean follow-up of 15 months, there was a recurrence in the regional lymph nodes in the patient with lymphatic vessel infiltration 18 months after ESD. This was considered to be nonresectable and the patient was followed up with CT every 6 months and annually with endoscopic ultrasonography (no further details given). | | chromoendoscopy, endoscopic biopsy, and for lesions with suspicion of submucosal invasion, endoscopic ultrasonography<br>• It is not clear why the number of lesions reported to have been 'HGIN', m1, m2, m3, sm1 and sm2 adds up to 68, rather than 58. |

Abbreviations used: CI, confidence interval; CT, computerised tomography; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; HGIN, high-grade intraepithelial neoplasm; IV, intravenous; M, mucosal; OR, odds ratio; PPI, proton pump inhibitor; OSCC, oesophageal squamous cell carcinoma; SM, submucosal

| Study details | Key efficacy findings | Key safety findings | Comments |
|---|---|---|---|
| Mizuta H (2009)[6]<br><br>**Case series**<br>Japan<br>Recruitment period: 2003–2008<br>Study population: patients with superficial OSCC<br>n = **33 (42 lesions)**<br>Mean age: 67.5 years<br>Sex: 85% male<br>Location: cervical oesophagus (3), upper thoracic (3), middle thoracic (20), lower thoracic (16)<br>Appearance: depressed (10), flat (23), elevated (9)<br>Depth: carcinoma in situ- lamina propria mucosae (29), muscularis mucosae – sm1(9), muscularis propria – sm2 (4)<br><br>Exclusion criteria: histologically shown adenocarcinoma arising from Barrett's oesophagus, patients treated with additional treatments before or immediately after ESD<br><br>Technique: ESD<br><br>Follow-up: **not reported**<br><br>Conflict of interest/source of funding: not reported | Efficacy not reported | Number of patients analysed: **33 (42 lesions)**<br><br>***Complications*** — **No. of lesions (%)**<br>Delayed bleeding — 0<br>Major perforation (endoscopically confirmed during ESD) — 2 (4.8)<br>Minor perforation (if mediastinal emphysema or a small amount of free air observed in chest CT with no endoscopic finding of perforation)* — 3 (7.1)<br>Mediastinitis (mediastinal effusion on chest CT with pyrexia and or/leukocytosis) — 2 (4.8)**<br>Stenosis in patients presenting with dysphagia (when 9.8 mm endoscope was unable to pass through)*** — 7 (16.7)<br><br>* not accompanied by mediastinitis<br>** these patients were also 2 of the patients with major perforation<br>***timing not reporting; successfully treated with balloon dilatation in an outpatient clinic for 6 patients; 1 patient did not respond but the dysphagia finally resolved with another balloon dilation 6 months after ESD.<br><br>***Predictive factors for post-ESD stenosis***<br>Of the 7 patients with stenosis, tumour size (both circumferential and longitudinal) was significantly greater than the 35 patients who did not develop stenosis ($p < 0.001$ and $p = 0.003$).<br>The size of dissected area in the mucosa was also significantly greater in those who developed stenosis compared with those who did not develop stenosis (p | **Follow-up issues**:<br>• Peripheral blood count and chest X-ray on day 1 and 3; if low haemoglobin endoscopy checked for bleeding; CT scan if patient showed clinical signs suggesting perforation or mediastinitis.<br>• Routine gastroendoscopy from 2 to 4 weeks after ESD<br><br>**Study design issues**:<br>• Retrospective review of consecutive patients treated at a centre.<br>• It was not reported how these patients were selected for endoscopic resection over surgery.<br>• Purpose to review complications and look at factors between cases with and without stenosis.<br><br>**Other issues**<br>• All patients were confirmed histologically as SSC. |

| Abbreviations used: CI, confidence interval; CT, computerised tomography; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; HGIN, high-grade intraepithelial neoplasm; IV, intravenous; M, mucosal; OR, odds ratio; PPI, proton pump inhibitor; OSCC, oesophageal squamous cell carcinoma; SM, submucosal | | | |
|---|---|---|---|
| **Study details** | **Key efficacy findings** | **Key safety findings** | **Comments** |
| | | < 0.001).<br>Histopathology, location, lymphatic invasion, venous invasion, occurrence of perforation and en bloc resection were not statistically significant in these groups. | |

Abbreviations used: CI, confidence interval; CT, computerised tomography; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; HGIN, high-grade intraepithelial neoplasm; IV, intravenous; M, mucosal; OR, odds ratio; PPI, proton pump inhibitor; OSCC, oesophageal squamous cell carcinoma; SM, submucosal

| Study details | Key efficacy findings | Key safety findings | Comments |
|---|---|---|---|
| Kakushima N (2006)[7]<br><br>**Case series**<br>Japan<br>Recruitment period: 2000–2005<br>Study population: patients with tumours of the oesophogastric junction<br>n = **30**<br>Mean age: 70 years<br>Sex: TBD<br>Histopathology: I+IIa (1), IIa (11), IIa+IIb (1), IIa+IIc (3), IIc (13), IIc+III (1); adenoma (5), adenocarcinoma (25; 4 were Barrett's adenocarcinoma)<br>Location: TBD<br>Depth: p-T1m (13), p-T1sm, submucosa < 500 µm (7), p-T1sm, submucosa ≥500 µm (5)<br>Vessel infiltration of carcinoma (5)<br>Mean diameter of lesion: 22.4 mm<br>Mean resected diameter: 40.6 mm<br><br>Exclusion criteria: squamous cell carcinoma<br><br>Technique: ESD with glycerin solution with normal saline plus fructose and high-molecular-weight hyaluronic acid; postoperative administration of sucralfate and a PPI until 8 weeks after the procedure<br>Mean follow-up: **14.6 months (in 28 patients followed up for > 6 months)**<br><br>Conflict of interest/source of funding: none | Number of patients analysed: **30**<br><br>Mean procedure time: 70 minutes<br><br>***Completeness of resection***<br>En bloc curative resection (with free margins) was 97% (29/30).<br>The person with non curative resection had a vertical margin positive for tumour (subsequent treatment not reported).<br>***Local recurrence***<br>No local recurrence at mean 14.6 month follow-up in the 28 patients followed up for more than 6 months. | 1 small perforation detected during ESD which was safely managed by rotatable clips and antibiotics. No pneumoperitoneum detected on radiography.<br><br>1 case of postoperative stenosis successfully managed with balloon dilation in an outpatient clinic on 3 occasions<br><br>No blood transfusions required or emergency endoscopy. | **Follow-up issues**:<br>• Follow-up endoscopy at 1 week and then discharged.<br>• 2, 6, and 12 month follow-up with endoscopy (curative patients); those with noncurative resection who did not wish to have additional surgery had close follow-up by CT and endoscopy every 6 months indefinitely.<br><br>**Other issues**:<br>• Preoperative endoscopy, chromoendoscopy and biopsy to determine indication. |

Abbreviations used: CI, confidence interval; CT, computerised tomography; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; HGIN, high-grade intraepithelial neoplasm; IV, intravenous; M, mucosal; OR, odds ratio; PPI, proton pump inhibitor; OSCC, oesophageal squamous cell carcinoma; SM, submucosal

| Study details | Key efficacy findings | Key safety findings | Comments |
|---|---|---|---|
| Chiu PW (2008)[10]<br><br>**Case series**<br>Japan<br>Recruitment period: 2004–2006<br>Study population: patients with stage IIb oesophageal cancer<br>n = **7**<br><br>Mean age: 64.7 years<br>Sex: 71% male<br>Histopathology: 4 moderate dysplasia, 2 mild dysplasia and 1 squamous cell carcinoma<br>Mean tumour size: 11.7 mm<br><br>Patient selection criteria: diagnosis of superficial oesophageal neoplastic lesions diagnosed as dysplasia or well- or moderately differentiated adenocarcinoma on biopsy<br>Exclusion criteria: definite invasion of submucosa, signet ring cell or poorly differentiated carcinoma<br><br>Technique: ESD followed by oral PPIs for 72 hours<br><br>Mean follow-up = **22.3 months**<br><br>Conflict of interest/source of funding: Instruments provided by Olympus Co. Ltd. | Number of patients analysed: **7**<br><br>Mean procedure time: 86.6 minutes<br><br>***Completeness of resection***<br>R0 resection (with with no involvement of margin) in all patients.<br><br>***Local recurrence***<br>No local recurrence at a mean follow-up of 22.3 months. | ***Complications***<br>There were no perforations.<br>One patient had a reactionary haemorrhage 12 hours after the procedure (not stated if this was in a patient treated for an oesophageal or a gastric lesion). This was successfully treated with endoscopic injection of epinephrine and endoscopic clips.<br>One death 2 years later from tuberculosis and bilateral pleural effusion (indication not reported). | **Follow-up issues**:<br>• Follow-up endoscopy every 3 months for the first year and then annually.<br><br>**Study design issues**:<br>• This study also included 25 patients with gastric neoplasia.<br>• Patients were selected for this procedure if they fulfilled the inclusion criteria<br>• The study reports the usage of various combinations of instruments.<br><br>**Other issues**<br>• Preoperative staging was competed by endoscopic ultrasonography. |

| Abbreviations used: CI, confidence interval; CT, computerised tomography; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; HGIN, high-grade intraepithelial neoplasm; IV, intravenous; M, mucosal; OR, odds ratio; PPI, proton pump inhibitor; OSCC, oesophageal squamous cell carcinoma; SM, submucosal | | | |
|---|---|---|---|
| **Study details** | **Key efficacy findings** | **Key safety findings** | **Comments** |
| Ikeda K (2009)[8]<br><br>**Case report**<br>Japan<br>Recruitment period: not reported<br>Study population: 73 year old male with short segmental Barrett's oesophagus and slightly depressed, discolored lesion on the anterior wall of the lower oesophagus<br>n = **1**<br><br>Technique: ESD with glycerin and fructose solution<br><br>Follow-up: **6 months**<br><br>Conflict of interest/source of funding: not reported | Number of patients analysed: **1**<br><br>***Completeness of resection***<br>The patient had en-bloc resection of Barrett's oesophagus with clear margins.<br>Histopathological examination from the resected area confirmed intramucosal well-differentiated tubular adenocarcinoma adjacent to the muscularis mucosae with no angiolymphatic invasion.<br><br>***Local recurrence***<br>No recurrence or metachronous lesions at 6 months | No complications. | **Follow-up issues**:<br>• Oesophagectomy was repeated at 6 months.<br><br>**Other issues**:<br>• With preoperative diagnosis with chromoendoscopy, the patient was classified as IIb+IIc (differentiated adenoma was suspected). Endoscopic ultrasound and computer tomography was used to exclude lymph node metastases. |

## *Efficacy*

### Completeness of resection

A comparative case series of 136 patients (171 lesions with OSCC ≤20mm) reported an en-bloc resection rate of 100% (31/31) in lesions treated with ESD, 87% (59/68) in lesions treated with EMR with a transparent cap and 71% (51/72) in lesions treated with 2-channel EMR (ESD and 2-channel EMR were significantly different; $p < 0.05$). The curative resection rate (defined as en-bloc with tumour-free margins, no lymph involvement and a tumour invasion to a depth from the first mucosal layer to the first submucosal layer) was 97% (30/31), 71% (48/68) and 46% (33/72), respectively, in these groups ($p < 0.05$ in comparison to both other groups)[1].

A comparative case series of 77 patients with lesions of OSCC ≤20 mm reported en-bloc resections in 90.6% (29/32) of lesions treated by ESD and 10.9% (5/46) of lesions treated by EMR (total of 78 lesions in 70 patients since 7 patients were lost to follow-up: 1 in ESD group and 6 in EMR group)[2].

Case series of 84 patients (107 squamous neoplastic or dysplastic lesions) and 43 patients (58 squamous neoplastic or dysplastic lesions) reported en-bloc resection of all lesions and R0 resection in 88% (94/107) and 78% (45/58) of lesions, respectively[3,9]. In the study of 84 patients, fifteen (18%) had possible node-positive tumours so underwent further treatment such as oesophagectomy or radiation therapy (with or without chemotherapy)[3].

A case series of 102 cases of OSCC treated by ESD reported en-bloc resection in 93% (95/102) of cases (it was not clear in the study if 'case' referred to patients or lesions or if this figure includes accuracy of margins)[4].Case series of 30 patients (5 adenoma, 25 adenocarcinoma) and 7 patients (6 dysplasia, 1 OSCC) reported R0 resection in 97% (29/30) and 100% (7/7) of patients, respectively[7,10]. The person with non curative resection in the first study had a vertical margin positive for tumour (subsequent treatment not reported).

### *Local recurrence / distant metastases*

The comparative case series of 136 patients with ≤20mm OSCC lesions reported no recurrences in the patients treated with ESD (time of follow-up not reported; 2 patients treated with 2-channel EMR had local recurrence successfully treated with either EMR with a transparent cap or 2-channel EMR)[1].

The comparative case series of 77 patients with OSCC, reported local recurrence in 4% (1/26) of patients treated by ESD and 25% (11/44) of patients treated with EMR (level of significance and time of occurrence not reported). All patients with recurrence had been treated in a piecemeal fashion and had superficial cancers and were subsequently treated with repeat EMR or endoscopic coagulation therapy resulting in remission in 10 patients. One patient had another local

recurrence requiring endoscopic resection and 'chemoradiation' therapy and another chose to have surgery for subsequent treatment. At a median follow-up of 38 months after the last therapy, 75% (9/12) were still alive without further occurrence (3 died of other diseases)[2].

The case series of 84 patients reported 1 local recurrence, which occurred at 6 months in a lesion preoperatively diagnosed as high-grade dysplasia (referred to in the source as 'high-grade intraepithelial neoplasm' [HGIN]). In the 56 patients with follow-up longer than a year, 20% (11/56) required more than 1 ESD session for neoplasms believed to be synchronous (i.e. diagnosed at the same time as the 'index' tumour) and 2 had a second ESD procedure for neoplasms believed to be metachronous (i.e. diagnosed as new neoplasms after the index tumour was diagnosed) at 13- and 17-month follow-up[3].

The same study reported distant metastases in 2 patients who had originally presented with layer 3 infiltration of the mucosa at 8- and 18-month follow-up (1 of these presented with vessel infiltration and the other did not; location of metastases and subsequent treatment not reported).

The case series of 102 cases reported that there were no cases of local recurrence of OSCC in a mean follow-up of 21 months[4].

The case series of 43 patients reported local recurrence in one of the 22 patients who were determined preoperatively to have node-negative lesions and were followed-up for longer than 6 months (mean follow-up period 17 months). This occurred 6 months after the procedure in a patient with Rx resection which was not evaluable for lateral margins and was successfully treated with another ESD procedure. There was no further local recurrence in an additional 12 months of follow-up[9].The same study reported local recurrence in one of 18 lesions (16 patients) which were determined preoperatively to have risk of lymph node metastases during a mean follow-up of 15 months. The recurrence, which occurred in a patient who originally presented with lymphatic vessel infiltration, occurred in the regional lymph nodes 18 months after the procedure. This was considered nonresectable and the patient was scheduled for further follow-up (no further details about the patient's outcome was described)[9].

Case series of 30 and 7 patients and one case report (one patient) including mostly patients with dysplasia, adenoma or adenocarcinoma reported no local recurrence at follow-ups of 14.6 months, 22.3 months and 6 months, respectively[7,10,8].

***Survival***

The case series of 84 patients treated for squamous neoplasia or dysplasia reported that 3 patients died from oeosophageal cancer during the follow-up period of median 632 days. The 5-year overall survival rates were 95% in the 77 patients with high-grade dysplasia (referred to as 'HGIN' in the source) or m2 and

100% in those with m3 or sm. The 5-year cause-specific survival rate was 56% in the 77 with high-grade dysplasia or m2 and 85% in those with m3 or sm (rates were significantly higher for those with m3 or sm; $p \leq 0.05$)[3].

## *Safety*

### Oesophageal perforation

The comparative case series of 136 patients reported a perforation during the procedure causing mediastinal emphysema in 1 patient during ESD; this was successfully treated by antibiotics[1].

The comparative case series of 77 patients reported mediastinal emphysema after the procedure in 8% (2/26) of patients treated with ESD which was later determined by radiography to be because of microperforation or air passage through a gap of muscle fiber. Neither had respiratory symptoms and both recovered within 3 days with antibiotic administration[2].

The case series of 84 patients treated by ESD reported perforation detected during the procedure by endoscopy (resulting in mediastinal emphysema) in 5% (4/84) of patients. All were immediately treated successfully with endoscopic clips; patients were given antibiotics and not allowed to eat or drink for several days[3].

The case series with 102 cases reported mediastinal emphysema in 6% (6/102) of cases, which were treated successfully with antibiotics and fasting with IV infusion (time of occurrence not reported)[4]. The authors also indicate in the study that there were no perforations – they may mean no perforations identified during the procedure, i.e. it may be that the reported mediastinal emphysema occurrences relate to 'occult' perforations not identified during the procedure.

The case series of 43 patients reported perforation with pneumomediastinum in 7% (4/58) of lesions which were successfully treated with endoscopic clipping (all cases of pneumomediastinum resolved spontaneously within a week; time of occurrence not reported)[9]. A case series of 33 patients reported perforation detected endoscopically during ESD in 5% (2/33) of patients and perforation detected after the procedure (based on the presence of mediastinal emphysema or air in chest computerised tomography) in 7% (3/33) of patients. Two of the patients with endoscopically detected perforation had mediastinitis[6].

The case series of 30 patients reported a small perforation detected during the procedure which was successfully treated by rotatable clips and antibiotics[7].

### Oesophageal stenosis/stricture

The comparative case series of 136 patients reported no postoperative strictures in patients treated with ESD and 3 in patients treated with EMR plus a

transparent cap (successfully treated by endoscopic balloon dilation; time of occurrence not reported).

The comparative case series of 77 patients reported postoperative stricture 24% (17/70) of patients treated by EMR or ESD. Each were successfully treated with endoscopic balloon dilation (time of occurrence not reported)[2].

The case series of 102 cases reported stenosis requiring balloon dilatation in 7% (7/102) of cases. These patients required ESD in four fifths or more of the circumference of the oesophgaus[4].

A case series of 65 patients with high-grade dysplasia (referred to as 'HGIN' in the source) or squamous carcinoma in layer 2 of the mucosa reported stricture in 17% (11/65) of patients. Each was treated with between 1 and 19 sessions of balloon dilatation over a period of 0–47.3 months. Four required less than 5 dilatations and 4 required more than 15. The period between dilatations was up to 12 months[5].

In the same study, univariate analysis showed that the patients who developed stricture had significantly longer circumferential extent of the lesion, histologic depth, procedure time and both longitudinal diameter and circumferential diameter ($p < 0.0001$, $p = 0.0002$, $p = 0.0069$, $p = 0.0062$ and $p = 0.002$, respectively). Multivariate analysis of these 5 variables revealed that both lesions extending to more than three quarters of the circumferential area (OR 44.2, 95% CI 4.4 to 443.6, $p = 0.0002$) and a histological depth to m2 (OR 14.2, 95% CI 2.7 – 74.2, $p = 0.0002$) were associated with a high rate of postoperative stricture.

The case series of 43 patients reported stricture successfully treated with balloon dilation in 16% (9/58) of lesions. In 7 of these occurrences, the lesions covered more than three quarters of the circumference of the oesophagus (time of occurrence not reported)[9].

The case series of 33 patients reported that 17% (7/33) of patients presented with dysphagia and were determined to have stenosis. This was treated by balloon dilation successfully in 6 patients. One patient required another balloon dilation 6 months after the procedure in order to relieve the dysphagia. The same study reported that circumferential and longitudinal tumour size were significantly greater in patients who developed stenosis than those who did not ($p < 0.001$ and $p = 0.003$, respectively)[6].

The case series of 30 patients reported 1 case of postoperative stenosis which was successfully managed with balloon dilation in an outpatient clinical on 3 occasions (time of occurrence or treatment not reported)[7].

## *Validity and generalisability of the studies*

- The great majority of the published evidence relates to OSCC tumours, located in the middle or upper part of the oesophagus. In table 2 of this overview, both comparative case series and 5 case series predominantly include patients with OSCC and some with high-grade dysplasia (referred to as 'HGIN' in most of the papers) (approximately 540 patients)[1,2,3,4,5,6,9]. This sharply contrasts with the epidemiology of oesophageal cancer in the UK, with a distribution of about 40%:60% between squamous cell and OAC tumours respectively – the latter type being predominantly found in the lower oesophagus. Table 2 of this overview includes 4 studies with approximately 37 patients treated for dysplasia, adenoma or adenocarcinoma[7,8,10].
- In addition, most of the patients have presented in very early stage – this is unusual in the UK.
- The above two factors limit the external validity (generalisability) of the evidence in the UK setting.
- There is 1 European trial of ESD for upper GI lesions which treated 2 patients with oeosophageal lesions (this study is in appendix A).
- Patient selection is unclear in the evidence base (for example, why an endocopic surgery was performed over surgery).
- The evidence consists mainly of case series including some comparison with EMR. Patient selection between EMR and ESD may depend on the size of the lesion so differences in the results may not be true comparisons. The first study in this overview specifically compares only lesions ≤20 mm in an attempt to provide a more accurate comparison between techniques.
- The length of follow-up in the studies ranged up to a period of 38 months, but details of endoscopic (biopsy) protocols (in terms of interval and number of endoscopic follow-up investigations) for some studies is unclear.
- All but 1 study reported how the patients were pre-diagnosed before treatment (most were histologically confirmed but some studies used preoperative chromoendoscopy).

- There is some duplicate reporting of patients in a number of the studies. Where this is suspected, it has been reported in the 'comments' section.
- In order to manage the volume of search results, the literature search was restricted to papers published after 1999 to help focus on evidence using current versions of the technique.

### *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**

- Photodynamic therapy for high-grade dysplasia in Barrett's oesophagus. NICE interventional procedures guidance 82 (2004). Available from www.nice.org.uk/IPG82
- Thoracoscopically assisted oesophagectomy. NICE interventional procedures guidance 189 (2006). Available from www.nice.org.uk/IPG189
- Circumferential radiofrequency ablation for Barrett's oesophagus. NICE interventional procedures guidance 310 (2007). Available from www.nice.org.uk/IPG310

## 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.

Mr Grant Fullarton, Mr John Wayman, Association of Upper Gastrointestinal Surgeons for Great Britain and Ireland, Dr Pradeep Bhandari, Dr Krish Ragunath, Mr Sami Shimi, British Society of Gastroenterology

- Oesophagectomy or endoscopic mucosal resection is the comparator.
- Key efficacy outcomes include adequacy of cancer treatment (complete pathological resection of margins), local and metastatic recurrence and survival.

- The Advisers considered theoretical adverse events to include aspiration pneumonia, uncontrollable bleeding, need for emergency oesophagectomy, stricture and scarring, and perforation and noted that the risk of these complications is likely to be related to experience or expertise.
- One Adviser highlighted that removing lesions completely is more difficult when they have invaded into the submucosa.
- The safety of the procedure is related to the experience and training of the surgeon and, since there are very few patients being treated with this procedure currently, endoscopists may not be able to maintain these skills.
- The use of a diathermy needle is a new technique for most endoscopists. Most practitioners who wish to use this attend and gain mentorship from an experienced centre (usually in Japan).
- The efficacy of this technique in a UK population is unclear.
- One Adviser commented that few patients will be indicated for this procedure since surgery is usually recommended in patients with very early cancer and who are fit enough. In patients not fit for surgery, the risks of the procedure may not be justified.
- This procedure needs to be carefully audited in the UK in high-volume tertiary referral centres with access to an oesophageal cancer surgeon, should be performed by appropriately trained staff and patient care must be managed through a multi-disciplinary team.

## Patient Commentators' opinions

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

## Issues for consideration by IPAC

- See validity and generalisability section.

# References


1. Ishihara R, Iishi H, Uedo N et al. (2008) Comparison of EMR and endoscopic submucosal dissection for en bloc resection of early esophageal cancers in Japan. Gastrointestinal endoscopy 68:1066–72.

2. Ishihara R, Iishi H, Takeuchi Y et al. (2008) Local recurrence of large squamous-cell carcinoma of the esophagus after endoscopic resection. Gastrointestinal endoscopy 67:799–804.

3. Ono S, Fujishiro M, Niimi K et al. (2009) Long-term outcomes of endoscopic submucosal dissection for superficial esophageal squamous cell neoplasms. Gastrointestinal endoscopy 70:860–6.

4. Oyama T, Tomori A, Hotta K et al. (2005) Endoscopic submucosal dissection of early esophageal cancer. Clinical gastroenterology and hepatology 3:S67–70.

5. Ono S, Fujishiro M, Niimi K et al. (2009) Predictors of postoperative stricture after esophageal endoscopic submucosal dissection for superficial squamous cell neoplasms. Endoscopy 41:661–5.

6. Mizuta H, Nishimori I, Kuratani Y et al. (2009) Predictive factors for esophageal stenosis after endoscopic submucosal dissection for superficial esophageal cancer. Diseases of the esophagus 22:626–31.

7. Kakushima N, Yahagi N, Fujishiro M et al. (2006) Efficacy and safety of endoscopic submucosal dissection for tumors of the esophagogastric junction. Endoscopy 38:170–174.

8. Ikeda K., Isomoto H, Oda H et al. (2009) Endoscopic submucosal dissection of a minute intramucosal adenocarcinoma in Barrett's esophagus. Digestive Endoscopy 21:34–36.

9. Fujishiro M, Yahagi N, Kakushima N et al. (2006) Endoscopic submucosal dissection of esophageal squamous cell neoplasm. Clinical gastroenterology and hepatology 4:688–94.

10. Chiu PW, Chan KF, Lee YT et al. (2008) Endoscopic submucosal dissection used for treating early neoplasia of the foregut using a combination of knives. Surgical Endoscopy 22:777–3.

# Appendix A: Additional papers on endoscopic submucosal dissection of oesophageal dysplasia and neoplasia

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 |
|---|---|---|---|
| Chaves DM, Maluf Filho F, de Moura EG et al. (2010) Endoscopic submucosal dissection for the treatment of early esophageal and gastric cancer - initial experience of a western center. Clinics (Sao Paulo, Brazil) 65:377-82. | Case series<br>n = 6 with squamous carcinoma<br>Mean follow-up = 9 months | All had free lateral and deep margins.<br>No residual tumours or recurrences in follow-up.<br>2 cases of pneumomediastinum | Larger studies are included in table 2. |
| Fujishiro M, Yahagi N, Kakushima N et al. (2006) En bloc resection of a large semicircular esophageal cancer by endoscopic submucosal dissection. Surgical Laparoscopy, Endoscopy and Percutaneous Techniques 16:237–1. | Case report<br>n = 1 (squamous cell carcinoma)<br>Follow-up = 6 months | Semicircular squamous cell carcinoma treated successfully en-bloc with no complication in a patient being treated with esophagogastroduodenoscopy.<br>At 6 months, mild stenosis was present but dilation not required. | Larger studies are included in table 2. |
| Fujishiro M, Kodashima S. (2009) Indications, techniques, and outcomes of endoscopic submucosal dissection for esophgaeal squamous cell carcinoma. Esophagus 6:143–8. | Case series<br>n = 81 (104 high grade dysplasia ['HGIN'] lesions)<br>Follow-up = not reported | Includes patients as Ono 2009 in table 2. | Includes patients as Ono 2009 in table 2. |
| Fujita Y, Hiramatsu M, Kawai M et al. (2008) Successful treatment for hypopharyngeal cancer in a patient with superficial esophageal cancer by endoscopic submucosal dissection. Endoscopy 40 Suppl-90. | Case report<br>n = 1<br>Follow-up = not reported | Successful treatment of hypopharyngeal cancer in patient treated for superficial oesophageal cancer. | Larger studies are included in table 2. |
| Hata K, Andoh A, Hayafuji K et al. (2009) Usefulness of bispectral monitoring of conscious sedation during endoscopic mucosal dissection. World journal of gastroenterology 15:595–8. | Case series<br>n = 13 with early-stage oesophageal cancer<br>No follow-up reported (purpose was to report safety) | Of 366 cases treated in the gastrointestinal tract, 13 cases had adverse events: 6 bradycardia, 2 respiratory depression, 4 decreased blood pressure and 1 delayed awakening.<br>These events were not separated out by indication. | Safety events are not reported, separated out by indication so it is difficult to determine how many of the patients with oesophageal lesions suffered from the events. Also, larger studies are included in table 2. |

| | | | |
|---|---|---|---|
| Hulagu S, Senturk O, Aygun C et al. (2007) Granular cell tumor of esophagus removed with endoscopic submucosal dissection. Turkish Journal of Gastroenterology 18: 188–191. | Case report<br>n = 1 granular cell carcinoma<br>Follow-up = not reported | Description of removal successfully. | Larger studies are included in table 2. |
| Maruyama K, Motoyama S, Sato Y et al. (2008) Surgical and nonsurgical management of perforation complicating endoscopic submucosal dissection of esophageal cancer: report of three cases. Esophgaus 5:215–8. | Multiple case report<br>n = 3 (all 0-IIc squamous cell carcinoma)<br>Follow-up not reported. | Each event occurred during ESD and was successfully treated. One by drainage of the mediastinal abscess under thoracoscopy, one by mediastinal drainage from the cervix and the first with endoscopic clips. | Larger studies are included in table 2. |
| Motohashi O, Nishimura K, Nakayama N et al. (2009) Endoscopic submucosal dissection (two-point fixed ESD) for early esophageal cancer. Digestive Endoscopy 21: 176–179. | Case series<br>n = 9 (intramucosal early oesophageal cancer > 20 mm)<br>Mean follow-up = 12 months | Complete tumour resection: 100%<br>Median mucosal resection size: 30 mm<br>Median size of cancer: 27 mm<br>No local recurrence or perforations. | Larger studies are included in table 2. |
| Probst A, Golger D, Arnholdt H et al. (2009) Endoscopic submucosal dissection of early cancers, flat adenomas, and submucosal tumors in the gastrointestinal tract. Clinical Gastroenterology & Hepatology 7:149–155. | Case series<br>n = 2 early oesophageal squamous cell (51 gastric, 17 rectal, 1 duodenal)<br>Follow-up = 14.4 months | Both were resected en bloc with 30 mm diameter of resection each.<br>No recurrence or complications in those treated for oesophageal lesions. | Larger studies are included in table 2. |
| Repici A, Hassan C, Carlino A et al. (2010) Endoscopic submucosal dissection in patients with early esophageal squamous cell carcinoma: results from a prospective Western series. Gastrointestinal Endoscopy 71:715–721. | Case series<br>n = 20 with OSCC lesions (mean size 32 mm)<br>Median follow-up = 18 months | En-bloc with resection free margins in 18.<br>2 had incomplete or indeterminate resection.<br>2 cases of mediastinal emphysema without overt perforation and 1 of post-ESD symptomatic stricture.<br>No local or distant recurrence. | Larger studies are included in table 2. |
| Saito Y, Takisawa H, Suzuki H et al. (2008) Endoscopic submucosal dissection of recurrent or residual | Case series<br>n = 4 patients with local recurrence of squamous cell carcinoma (3 stage I, 1 | Tumour-free margins from histopathology examination in 3 of 4 patients.<br>Mean tumour size of resected specimens: 35 mm. | Larger studies are included in table 2. |

| | | | |
|---|---|---|---|
| superficial esophageal cancer after chemoradiotherapy. Gastrointestinal Endoscopy 67:355–359. | stage II)<br>after chemoradiotherapy<br>Median follow-up = 3 months | No recurrence or distant metastases.<br>No complications. | |
| Saito Y, Tanaka T, Andoh A et al. (2008) Novel biodegradable stents for benign esophageal strictures following endoscopic submucosal dissection. Digestive diseases and sciences 53:330–3. | Multiple case report<br>n = 2 patients with benign oesophageal stenosis after ESD for squamous cell carcinoma<br>Follow-up = 6 months | The patients were treated with a new biodegradable stent.<br>Neither have any symptoms of stenosis at 6 months.<br><br>3 with CRT then ESD | Larger studies are included in table 2. |
| Saito Y, Tanaka T, Andoh A et al. (2007) Usefulness of biodegradable stents constructed of poly-/-lactic acid monofilaments in patients with benign esophageal stenosis. World journal of gastroenterology 13:3977–80. | Case series<br>n = 7 with oesophgeal cancer with stenosis after ESD<br>Follow-up = 7 months to 2 years | Treatment 2 to 3 days after ESD.<br>Spontaneous migration in 10 stents from 10 to 21 days after placement (no obstructive complication in these patients).<br>No symptoms or re-stenosis at follow-up and no balloon dilation required. | Larger studies are included in table 2. |
| Suzuki T, Nakajima Y, Nagai K et al. (2008) Case 1: superficial small cell carcinoma of the esophagus treated by chemotherapy combined with endoscopic submucosal dissection. Esophagus 5:230–232. | Case report<br>n = 1 squamous cell carcinoma | Description of patient treated with chemotherapy and ESD. Patient remains alive without tumour regrowth almost 2 years after the procedure. | Larger studies are included in table 2. |
| Toyonaga T, Nishino E, Dozaiku T et al. (2005) Use of short needle knife for esophageal endoscopic submucosal dissection. Digestive Endoscopy 17:246–252. | Case series<br>n = 20 (14 mucosal cancer, 5 submucosal cancer, 1 HGD)<br>Follow-up = not reported | All had complete en bloc resection.<br>Median resected specimen: 47 mm<br>There was one mediastinal emphysema | Larger studies are included in table 2. |

# Appendix B: Related NICE guidance for endoscopic submucosal dissection of oesophageal dysplasia and neoplasia

| Guidance | Recommendations |
|---|---|
| Interventional procedures | **Photodynamic therapy for high-grade dysplasia in Barrett's oesophagus. NICE interventional procedures guidance 82 (2004).**<br>1.1 Current evidence on the safety of photodynamic therapy for high-grade dysplasia in Barrett's oesophagus appears adequate to support the use of this procedure. Photodynamic therapy appears efficacious in downgrading dysplasia in Barrett's oesophagus, when used for the treatment of high-grade dysplasia (a premalignant lesion). However, its efficacy in preventing the progression of Barrett's oesophagus to invasive cancer is not clear.<br>1.2 Clinicians wishing to undertake photodynamic therapy for high-grade dysplasia in Barrett's oesophagus should take the following actions.<br>• Inform the clinical governance leads in their Trusts.<br>• Inform patients, as part of the consent process, about the uncertainty of influencing their long-term prognosis and provide them with clear written information. Use of the Institute's Information for the Public is recommended.<br>• Audit and review clinical outcomes of all patients having photodynamic therapy for high-grade dysplasia in Barrett's oesophagus.<br>1.3 Publication of long-term efficacy outcomes will be useful in reducing the current uncertainty. Randomised trials are in progress and clinicians are encouraged to consider entering patients into these (www.cancerhelp.org.uk/trials/trials/default.asp). The Institute may review the procedure upon publication of further evidence.<br>1.4 This guidance is limited to the procedure using pharmaceuticals licensed for photodynamic therapy of oesophageal dysplasia.<br><br>**Circumferential epithelial radiofrequency ablation for Barrett's oesophagus. NICE interventional procedures guidance 310 (2007).**<br>1.1 Evidence on the safety and efficacy of circumferential epithelial radiofrequency (RF) ablation for Barrett's oesophagus is currently inadequate. The evidence is limited in quantity and duration of follow-up and fails to justify the treatment of non- |

| | |
|---|---|
| | dysplastic Barrett's oesophagus. Therefore this procedure should only be used in the context of research.<br>1.2 Further research should specify clearly the grade of Barrett's oesophagus being treated and should include arrangements for long-term follow-up (for example, 5 years). The Institute may review the procedure upon publication of further evidence.<br><br>**Thoracoscopically assisted oesophagectomy. NICE interventional procedures guidance 189 (2006).**<br>1.1 Current evidence on the safety and efficacy of thoracoscopically assisted oesophagectomy appears adequate to support the use of this procedure, provided that normal arrangements are in place for consent, audit and clinical governance.<br>1.2 This procedure is technically demanding, and surgeons undertaking it should have special expertise and specific training in laparoscopic and thoracoscopic surgical techniques and should perform their initial procedures with an experienced mentor.<br>1.3 Patient selection and management should be carried out in the context of a multidisciplinary team that has a regular practice in open oesophagectomy.<br>1.4 Clinicians should submit data to the Minimally Invasive Gastro-Oesophageal Cancer Surgery (MIGOCS) National Database (www.e-dendrite.com/databases.htm) or the Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland (AUGIS) data set (www.augis.org/news/default.html). |

# Appendix C: Literature search for endoscopic submucosal dissection of oesophageal dysplasia and neoplasia

| Database | Date searched | Version/files |
|---|---|---|
| Cochrane Database of Systematic Reviews – CDSR (Cochrane Library) | 19/05/2010 | May 2010 |
| Database of Abstracts of Reviews of Effects – DARE (CRD website) | 19/05/2010 | N/A |
| HTA database (CRD website) | 19/05/2010 | N/A |
| Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library) | 19/05/2010 | May 2010 |
| MEDLINE (Ovid) | 19/05/2010 | 1950 to May Week 1 2010 |
| MEDLINE In-Process (Ovid) | 19/05/2010 | May 18, 2010 |
| EMBASE (Ovid) | 19/05/2010 | 1980 to 2010 Week 19 |
| CINAHL (NLH Search 2.0 or EBSCOhost) | 19/05/2010 | N/A |
| BLIC (Dialog DataStar) | 19/05/2010 | N/A |
| National Institute for Health Research Clinical Research Network Coordinating Centre (NIHR CRN CC) Portfolio Database | 15/12/2009 | None found. |
| Current Controlled Trials metaRegister of Controlled Trials - mRCT | 15/12/2009 | None found. |
| Clinicaltrials.gov | 15/12/2009 | None found |
| General internet search | 15/12/2009 | None found |
| Zetoc | 19/05/2010 | N/A |

Websites searched on 18/12/2009

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

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

endoscopy/ or exp endoscopy, digestive system/ or exp endoscopy, gastrointestinal/

endoscop*.tw.

duodenscop*.tw.

(endoscop* adj3 gastrointest*).tw.

Endoscopes/

or/1-5

submucos*.tw.

Intestinal mucosa/

7 or 8

exp Dissection/

(dissect* or resect*).tw.

microdissect*.tw.

or/10-12

6 and 9 and 13

ESD.tw.

14 or 15

((esophag* or oesophag*) adj3 (ulcer* or lesion* or adenoma* or polyp* or dysplas*)).tw.

Precancerous Conditions/

(precancer* or pre-cancer* or pre-malign* or premalign* or preneoplast* or pre-neoplastic*).tw.

((early or flat*) adj3 (neoplasm* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan*)).tw.

18 or 19 or 20

(esophag* or oesophag*).tw.

21 and 22

(neoplasm* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan*).tw.

(esophag* or oesophag*).tw.

24 and 25

Esophageal Neoplasms/

17 or 23 or 26 or 27

16 and 28

1999*.ed.

2000*.ed.

2001*.ed.

2002*.ed.

2003*.ed.

2004*.ed.

2005*.ed.

2006*.ed.

2007*.ed.

2008*.ed.

2009*.ed.

or/30-40

41 and 29

limit 42 to english language