# NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

## INTERVENTIONAL PROCEDURES PROGRAMME

## Interventional procedure overview of endoscopic mucosal resection and endoscopic submucosal dissection of non-ampullary duodenal lesions

This procedure can be used to treat abnormalities in the lining of the part of the small intestine near the stomach (the duodenum). A long camera (endoscope) is inserted through the mouth, oesophagus and stomach to view the affected area. A solution is injected into the wall of the duodenum, and then the abnormal parts of the lining are 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 March 2010.

## Procedure name

- Endoscopic mucosal resection and endoscopic submucosal dissection of non-ampullary duodenal lesions.

## Specialty societies

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

# Description

## *Indications and current treatment*

Duodenal lesions are rare. They include benign (hamartomatous), dysplastic (adenomatous) or neoplastic lesions (the latter could be either adenocarcinomas or carcinoid tumours). Some patients have inherited polyposis syndromes (such as familial adenomatous polyposis). Depending on lesion nature, size and location, patients may be asymptomatic or experience nausea and vomiting, loss of appetite and weight, anaemia and abdominal discomfort or pain. In patients with familial polyposis, lesions may be identified through regular surveillance examinations.

Treatment depends on lesion type and size. Current treatment of malignant lesions usually involves major surgery (Whipple procedure). However, during the last decade, endoscopic treatments such as snare polypectomy and argon plasma coagulation (APC) have been introduced as treatment options for smaller lesions.

*Lesion stage and morphology classifications*

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

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

For 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. Ulcerated lesions are characterised as 0-III.

## *What the procedure involves*

Both endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) aim to remove lesions without the need for abdominal surgery. In EMR, the lesion is usually removed piecemeal, whereas in ESD, the lesion is usually resected in one piece (en bloc). The latter has the

advantage of permitting a more accurate histopathological assessment and decreasing the risk of recurrence. Both procedures are technically difficult because the walls of the duodenum are thin and there is a risk of perforation.

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

In EMR, the lesion is then resected, usually piecemeal, with a snare. In ESD, submucosal dissection is performed with an electrocautery knife, parallel to the muscle layer, aiming to remove the lesion en bloc. A transparent hood may be used to retract the already dissected part of the lesion out of the field of view. In both procedures, an electrocautery knife is used to achieve haemostasis. Endoscopic clips may be used for larger vessels or to manage perforation. For a day or two postoperatively, patients can drink water before 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 mucosal resection and endoscopic submucosal dissection of non-ampullary duodenal lesions. Searches were conducted of the following databases, covering the period from their commencement to 19 May 2010: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

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

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

| Characteristic | Criteria |
|---|---|
| Publication type | Clinical studies were included. Emphasis was placed on identifying good quality studies.<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 non-ampullary duodenal lesions. |
| Intervention/test | Endoscopic mucosal resection and 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 86 patients from 6 case series (13 patients treated with ESD and 73 patients treated with EMR).

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 mucosal resection and endoscopic submucosal dissection of non-ampullary duodenal lesions

Abbreviations used: AF, atrial fibrillation; APC, argon plasma coagulation; CT, computerised tomography; FAP, familial adenomatous polyposis; GI, gastrointestinal; HGD, high-grade dysplasia; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; PPI, proton pump inhibitor; sm2/sm3, middle invasion in the submucosa (more than 200 µm below the muscularis mucosae; TVA, tubulovillous adenoma

| Study details | Key efficacy findings | Key safety findings | Comments |
|---|---|---|---|
| Ahmad NA (2002)[1]<br>**Case series**<br>USA<br>Recruitment period: 1997 – 2000<br>Study population: patients with duodenal lesions considered to be unresectable by standard snare techniques<br>n = **27 with duodenal lesion EMR (within a series of 92 patients with EMR of lesions in any GI organ, including oesophagus, stomach, colon, rectum and duodenum)**<br>Mean age: 65 (of all 92 patients treated for GI lesions)<br>Sex: 58% male (of all 92 patients treated for GI lesions)<br><br>Histopathology: HGD (2), adenoma (25)<br>Morphology: nodular (4), sessile (22), carpet-like (1)<br>Size: 1-4 cm<br>Patient selection criteria: patients with incomplete EMR at other institutions were included<br>Exclusion criteria: lesions showing malignant-appearing lymphadenopathy on endosonography<br>Technique: EMR (intravenous administration of glucagon was used to | Number of patients analysed: **27**<br><br>***Completeness of resection***<br>This was defined as complete removal based on endoscopic and pathological assessment and negative biopsy findings.<br>Complete resection was obtained in 85% (23/27) of patients<br>Of the 4 who had incomplete resection, 1 had tubulovillous adenoma on post-EMR pathology and 3 had adenomas with HGD. All patients underwent subsequent surgery, chemotherapy or endoscopic ablative therapy.<br>After EMR, 4 lesions were confirmed as HGD, 19 as adenoma, 2 as benign and 2 as carcinoid.<br>Three patients with a final diagnosis of HGD had initial biopsy or adenoma or non-neoplastic disease.<br><br>***Survival***<br>Only patients with HGD or adenocarcinoma on post-EMR findings and a complete resection were included in the survival analysis. This meant that only 1 patient with a treated duodenal lesion was included in the analysis (the other 3 with HGD had | ***Complications***<br>There were no perforations.<br>33% (9/27) of patients with EMR developed bleeding, but further details were only provided for the group of 22 patients of the whole series (n = 92) irrespective of the GI organ where EMR was performed:<br>73% (16/22) had early bleeding (within 24 hours) and 88% (14/16) of these required endoscopic treatment with clip placement (6), ligation with a detachable snare (1), monopolar electrocoagulation (6) and/or injection therapy (3).<br>27% (6/22) had delayed bleeding (after 24 hours) and 33% (2/6) of these required endoscopic management.<br>14% (3/22) patients required transfusions (it was not stated if these were patients with early or delayed bleeding). | **Follow-up issues**:<br>• Patients with compete excision of HGD or adenocarcinoma had follow-up with biopsy scheduled after 3 months; if negative, endoscopy repeated again at 3 months and then every 6 months.<br>• Results of follow-up were not given in the other 26 patients to describe whether or not they had recurrences.<br><br>**Study design issues**:<br>• This study was a retrospective case series of 92 consecutive patients (101 lesions) treated in the entire gastrointestinal tract (19 oesophagus, 14 stomach, 29 colon, 12 rectum, 27 duodenum).<br>• Patient selection was not described.<br><br>**Study population issues**:<br>• The study says that 28/92 patients had comorbid conditions, but this was not divided by location.<br><br>**Other issues**:<br>• Endoscopic ultrasound was performed preoperatively in 19 patients. |

Abbreviations used: AF, atrial fibrillation; APC, argon plasma coagulation; CT, computerised tomography; FAP, familial adenomatous polyposis; GI, gastrointestinal; HGD, high-grade dysplasia; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; PPI, proton pump inhibitor; sm2/sm3, middle invasion in the submucosa (more than 200 µm below the muscularis mucosae; TVA, tubulovillous adenoma

| Study details | Key efficacy findings | Key safety findings | Comments |
|---|---|---|---|
| inhibit peristalsis in some patients, enabling easier retrieval of lesions)<br>Follow-up: **not reported**<br>Conflict of interest/source of funding: not reported | incomplete resections). This patient was still alive at 45 months with no recurrence. | | |

Abbreviations used: AF, atrial fibrillation; APC, argon plasma coagulation; CT, computerised tomography; FAP, familial adenomatous polyposis; GI, gastrointestinal; HGD, high-grade dysplasia; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; PPI, proton pump inhibitor; sm2/sm3, middle invasion in the submucosa (more than 200 µm below the muscularis mucosae; TVA, tubulovillous adenoma

| Study details | Key efficacy findings | Key safety findings | Comments |
|---|---|---|---|
| Alexander S (2009)[2]<br><br>**Case series**<br>Australia<br>Recruitment period: 2002 - 2007<br>Study population: patients with large non-ampullary sessile duodenal lesions greater than 15 mm<br>n = **23**<br>Mean age: 62.2 years<br>Sex: 56.5% male<br><br>Exclusion criteria: polyposis syndrome<br><br>Technique: intravenous hyoscine was given to limit duodenal motility; EMR with sedation (duodenoscope for anteromedial lesions, paediatric colonoscope for lateral or posterior lesions); 8 lesions 15-20mm had en bloc resection and 13 with lesions greater than 20 mm had piecemeal resection; postoperatively, clear liquid diet for 1 day and PPI for 2 weeks<br><br>Median follow-up: **13 months**<br><br>Conflict of interest/source of funding: none | Number of patients analysed: **21**<br>In 2 patients, EMR was scheduled but not performed because both had very large lesions (40 and 60 mm) and had features suggestive of invasion: one had surgery confirming submucosal invasion and the other patient with a history of AF had a major cerebral ischaemic event before ultrasound could be performed.<br><br>***Completeness of resection***<br>Eight en bloc and 13 piecemeal. Eighteen patients successfully treated in a single session.<br>For a complete resection, 2 patients required 2 sessions and 1 required 3 sessions (additional sessions at 4 weekly intervals). These patients had extensive lesions with lesions more than two thirds the duodenal circumference.<br>Results of postoperative histological examination: 1 adenocarcinoma, 16 low-grade TVA, 3 high or focal high-grade TVA, 1 with both high-grade TVA and carcinoma (Size: 27.6 mm).<br><br>***Local recurrence (n = 20)***<br>Five lesions (25%; 5/20) had remnant adenoma (all were patients treated with piecemeal resection – 38.5% | ***Complications***<br>There were no perforations.<br><br>Two patients with continuing need for antiplatelet therapy for coronary stents had prophylactic closure of the defect with clips.<br>One patient had bleeding within 48 hours of the procedure and was treated successfully with endoscopic clips (no other details provided).<br>One patient was admitted overnight and given analgesia and intravenous antibiotics because of possible serositis. Abdominal CT scan showed normal results and the patient was discharged the next day. | **Follow-up issues**:<br>• Follow-up at 3 and 12 months and then annually.<br><br>**Study design issues**:<br>• This was a retrospective review of patients treated at a tertiary referral centre.<br>• Patients were referred from other centres, but the criteria for selection were not described (16 presented with no symptoms). Patients were reported to have been managed by a standardised technique before referral but this was not described.<br>• Resection in a single session was attempted in all but this was successful in 18; 2 required 2 sessions and 1 required 3 sessions.<br><br>**Study population issues**:<br>• Pre-operative symptoms included iron deficiency anemia (3), abdominal pain (2), nausea and vomiting (2), and some had no symptoms (16)<br><br>**Other issues**:<br>• The study did not make clear if the patients being treated had previous diagnosis of the lesion before treatment.<br>• Adequacy of resection (with or without clear margins) was not reported. |

| Abbreviations used: AF, atrial fibrillation; APC, argon plasma coagulation; CT, computerised tomography; FAP, familial adenomatous polyposis; GI, gastrointestinal; HGD, high-grade dysplasia; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; PPI, proton pump inhibitor; sm2/sm3, middle invasion in the submucosa (more than 200 µm below the muscularis mucosae; TVA, tubulovillous adenoma | | | |
|---|---|---|---|
| **Study details** | **Key efficacy findings** | **Key safety findings** | **Comments** |
| | [5/13]). All were treated successfully: 3 with snare resection (no submucosa injection) and APC and 2 with APC alone. All were clear at a median follow-up of 10 months. | | |

Abbreviations used: AF, atrial fibrillation; APC, argon plasma coagulation; CT, computerised tomography; FAP, familial adenomatous polyposis; GI, gastrointestinal; HGD, high-grade dysplasia; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; PPI, proton pump inhibitor; sm2/sm3, middle invasion in the submucosa (more than 200 µm below the muscularis mucosae; TVA, tubulovillous adenoma

| Study details | Key efficacy findings | Key safety findings | Comments |
|---|---|---|---|
| Oka S (2003)[3]<br><br>**Comparative case series**<br>Japan<br>Recruitment period: 1994 – 2001<br>Study population: early non-ampullary duodenal carcinoma (10 patients with sporadic carcinoma and 5 with FAP-associated carcinoma)<br>n = **15 (17 lesions: 13 EMR, 2 polypectomy, 2 open surgery)**<br>Mean age: 63.8 years (sporadic carcinoma), 34.9 years (FAP-associated carcinoma)<br>Sex: 90% male (sporadic carcinoma), 20% male (FAP-associated)<br>Location: first portion (7), second portion (8), third portion (2)<br>Depth: mucosal (15), submucosal (2)<br>Mean size: 13.2 mm (sporadic), 7.6 mm (FAP-associated carcinoma)<br>Patient selection criteria: not reported<br>Exclusion criteria: carcinoma of the ampulla of Vater<br><br>Technique: EMR, polypectomy and open surgery<br><br>Mean follow-up: **51.7 months**<br><br>Conflict of interest/source of funding: not | Number of patients analysed: **17 lesions (13 EMR, 2 polypectomy, 2 open surgery)**<br><br>***Local recurrence and survival***<br>At mean 51.7 months there were no deaths and no recurrence in any patient.<br><br>***Histological findings***<br>94% (16/17) well differentiated adenocarcinoma.<br>6% (1/17) of moderately differentiated adenocarcinoma.<br>50% (5/10) of sporadic carcinoma lesions and 57% (4/7) FAP-associated carcinoma lesions had adenomatous component around the cancer.<br>In the sporadic group, 1 had hyperplastic Brunner glands with elevated mucosa, one had submucosal invasion but the others were carcinoma in situ.<br><br>***Other characteristics of resected lesions***<br>Gross examination showed the following Paris macroscopic types:<br>EMR: IIa (8), IIc (4) Is (1)<br>Open surgery: Is (1), Isp (1)<br>Polypectomy: Isp (1), Ip (1) | ***Complications***<br>One patient had local bleeding after EMR, which was controlled with endoscopic clips.<br>No other complications. | **Follow-up issues**:<br>• Gastroduodenoscopy, endoscopic ultrasound, transabdominal ultrasound and CT were performed once every 6 to 12 months in the first year and then annually.<br>**Study design issues**:<br>• Retrospective.<br>• Tumours in patients with sporadic carcinoma were detected by gastroduodenoscopy at annual medical check ups (only 1 with epigastric pain was symptomatic). Tumours in patients with FAP-associated carcinoma were detected on routine surveillance at ages 20 and 25.<br>• 2 had open surgery instead of EMR because endoscopic evaluation was technically difficult. How patients were selected for EMR or polypectomy was not described (but it appears that most protruding tumours were treated with polypectomy or surgery).<br>• Results were not presented separately for those treated with surgery and polypectomy.<br>**Study population issues**:<br>• Patients with sporadic carcinoma were significantly older, had significantly larger tumours and were more likely to be men than those with FAP-associated carcinoma (frequent, early routine surveillance may explain the |

Abbreviations used: AF, atrial fibrillation; APC, argon plasma coagulation; CT, computerised tomography; FAP, familial adenomatous polyposis; GI, gastrointestinal; HGD, high-grade dysplasia; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; PPI, proton pump inhibitor; sm2/sm3, middle invasion in the submucosa (more than 200 µm below the muscularis mucosae; TVA, tubulovillous adenoma

| Study details | Key efficacy findings | Key safety findings | Comments |
|---|---|---|---|
| reported | | | age and tumour size difference).<br>**Other issues**:<br>• In lesions detected by endoscopic observation, a small tissue sample was used to determine the grade. Endoscopic ultrasound was performed in 3 patients with suspected submucosal invasion. |

Abbreviations used: AF, atrial fibrillation; APC, argon plasma coagulation; CT, computerised tomography; FAP, familial adenomatous polyposis; GI, gastrointestinal; HGD, high-grade dysplasia; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; PPI, proton pump inhibitor; sm2/sm3, middle invasion in the submucosa (more than 200 µm below the muscularis mucosae; TVA, tubulovillous adenoma

| Study details | Key efficacy findings | Key safety findings | Comments |
|---|---|---|---|
| Honda T (2009)[4]<br><br>**Case series**<br>Japan<br>Recruitment period: 2005 – 2008<br>Study population: superficial duodenal neoplastic lesions<br>n = **14 (9 ESD, 5 EMR) (15 lesions: 9 ESD, 6 EMR)**<br>Mean age: 60.7 years<br>Sex: 71% male<br>Location: descending portion (12 lesions), duodenal bulb (3 lesions)<br>Depth: all mucosal only<br><br>Patient selection criteria: not reported<br>Exclusion criteria: ampullary tumours<br><br>Technique: ESD and EMR with sodium hyaluronate<br><br>Follow-up: **not reported**<br><br>Conflict of interest/source of funding: not reported | Number of patients analysed: **14 (9 ESD, 5 EMR) (15 lesions: 9 ESD, 6 EMR)**<br><br>***Completeness of resection***<br>**ESD**<br>All 9 were resected en bloc (mean tumour size: 23.8 mm, mean resected specimen: 32.4 mm)<br>Results of histological exam: 5 carcinoma in adenoma, 4 high-grade adenoma.<br><br>**EMR**<br>Of the 6 lesions, all but one was en bloc (mean tumour size: 7.5 mm, mean resected specimen: 13.88 mm)<br>Results of histological exam: 1 high-grade adenoma and 5 low-grade adenoma. | ***Complications***<br><br>**ESD**<br>There were 2 perforations: 1 during ESD, treated successfully with an endoscopic clip and 1 delayed requiring surgical treatment (time of occurrence not reported).<br>There were 2 cases of postoperative bleeding requiring endoscopic haemostasis with clip therapy.<br><br>**EMR**<br>No patients had perforations but 1 with postoperative bleeding required haemostasis with endoscopic clip therapy. | **Follow-up issues**:<br>• Arrangements for follow-up not reported.<br>**Study design issues**:<br>• Patients were all those treated with endoscopic resection at the hospital. It is not clear how patients were selected for endoscopic resection.<br>• ESD was selected for larger and more challenging lesions.<br>• The technique used for EMR was not well described. One patient treated with EMR did not have circumferential pre-incision (it is not clear if this patient had submucosal injection to lift the lesion).<br>**Study population issues**:<br>• Patients treated with ESD had larger tumours than those treated with EMR.<br>**Other issues**:<br>• The authors commented that the rate of perforation for ESD was higher than in other parts of the gastrointestinal tract, largely because of abundant blood vessels in the submucosal layer and a thin muscle layer. They also commented that the risk of delayed perforation may be higher in the duodenum, partly from exposure to pancreatic juice and bile.<br>• The authors also commented that a large amount of skill is required for ESD in the duodenum but this may be difficult because it is rare. |

| Abbreviations used: AF, atrial fibrillation; APC, argon plasma coagulation; CT, computerised tomography; FAP, familial adenomatous polyposis; GI, gastrointestinal; HGD, high-grade dysplasia; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; PPI, proton pump inhibitor; sm2/sm3, middle invasion in the submucosa (more than 200 µm below the muscularis mucosae; TVA, tubulovillous adenoma | | | |
|---|---|---|---|
| **Study details** | **Key efficacy findings** | **Key safety findings** | **Comments** |
| | | | • Adequacy of resection (clear margins) with ESD was not reported. |

Abbreviations used: AF, atrial fibrillation; APC, argon plasma coagulation; CT, computerised tomography; FAP, familial adenomatous polyposis; GI, gastrointestinal; HGD, high-grade dysplasia; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; PPI, proton pump inhibitor; sm2/sm3, middle invasion in the submucosa (more than 200 µm below the muscularis mucosae; TVA, tubulovillous adenoma

| Study details | Key efficacy findings | Key safety findings | Comments |
|---|---|---|---|
| Takehashi T (2009)[5]<br><br>**Case series**<br><br>Japan<br>Recruitment period: 2007 – 2008<br>Study population: non-ampullary duodenal tumours<br><br>n = **4**<br><br>Mean age: 69 years<br>Sex: 50% male<br>Location: suprapapillary region (3), infrapapillary region (1)<br>Size: 10 – 31 mm<br>Macroscopic type: IIa (3), Ips (1)<br><br>Patient selection criteria: not reported<br><br>Technique: ESD<br>Mean follow-up: **18 months**<br><br>Conflict of interest/source of funding: none | Number of patients analysed: **4**<br><br>***Histological findings***<br>2 had well-differentiated adenocarcinoma and 2 had tubular adenoma with severe atypia.<br><br>***Local recurrence and survival***<br>All patients were alive with no local recurrences at a mean follow-up of 18 months. | ***Complications***<br>Perforation in 2 cases, which were resolved with close postoperative observation with antibiotics, use of a nasogastric tube and fasting.<br>In at least 1 of the 4 patients, 2 endoscopic clips were used to manage and prevent bleeding. | **Follow-up issues**:<br>• Gastrointestinal endoscopy and CT were used during follow-up but more details about arrangements for follow-up was not reported.<br><br>**Study design issues**:<br>• The study describes only how 2 of the patients were selected for ESD: 1 was detected on a health survey and the other had gastrointestinal endoscopy because of epigastralgia.<br><br>**Study population issues**:<br>• Three were asymptomatic, 1 had epigastric pain<br><br>**Other issues**:<br>• Chromoendoscopy was used to determine the extent of the lesions pre-operatively.<br>• Authors highlighted that indications for endoscopic treatment of duodenal lesions is not yet defined and agreed upon.<br>• The classification system used was not defined but it appears to be the Paris classification system. |

Abbreviations used: AF, atrial fibrillation; APC, argon plasma coagulation; CT, computerised tomography; FAP, familial adenomatous polyposis; GI, gastrointestinal; HGD, high-grade dysplasia; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; PPI, proton pump inhibitor; sm2/sm3, middle invasion in the submucosa (more than 200 µm below the muscularis mucosae; TVA, tubulovillous adenoma

| Study details | Key efficacy findings | Key safety findings | Comments |
|---|---|---|---|
| Waxman I (2002)[6]<br><br>**Case series**<br>USA and Japan<br>Recruitment period: not reported<br>Study population: patients with submucosal duodenal tumours<br>n = **3**<br>Age, sex and location of lesions: not reported<br><br>Depth: submucosal (2 sm3, 1 sm2)<br>Median tumour size: 9 mm<br>Patient selection criteria: lesion less than 2 cm diameter, no ulceration, no extension into muscularis propria<br>Exclusion criteria: lesion greater than 2 cm, bleeding diathesis<br><br>Technique: high-frequency probe endoscopic ultrasound-assisted EMR<br><br>Follow-up: **21.5 months (for all 28 patients treated with EMR for gastrointestinal lesions)**<br><br>Conflict of interest/source of funding: supported by a grant from Fijunon Photo Optica, Omiya, Japan | Number of patients analysed: **3**<br><br>***Completeness of resection***<br>All were resected with clear margins.<br><br>***Histological findings***<br>1 lipoma<br>2 carcinoid (a specimen could not be retrieved for 1 of these tumours; it is not clear how histology was determined in this patient).<br><br>***Local recurrence***<br>There was no recurrence during the follow-up period. | ***Complications***<br>None | **Follow-up issues**:<br>• Arrangements for follow-up not reported.<br><br>**Study design issues**:<br>• This study reports on EMR used to treat 28 patients with gastrointestinal lesions (3 oesophagus, 4 stomach, 3 duodenum, 18 colon).<br>• How patients were selected for treatment was not described.<br><br>**Other issues**:<br>• Pre-operative staging with endoscopy was completed to assess size, submucosal involvement and ultrasonographic characteristics of the lesions. |

## *Efficacy*

Efficacy and safety evidence presented in the overview relates to 6 studies and 86 patients, of whom 73 had EMR and 13 had ESD.

### Completeness of resection

A case series of 27 patients treated with EMR reported a complete resection in 85% (23/27) of patients. All 4 patients with incomplete resection underwent subsequent surgery, chemotherapy or endoscopic ablative therapy[1].

A case series of 23 patients with 21 patients treated with EMR (2 patients did not receive treatment because of possible submucosal invasion and a major cerebral ischaemic event) reported complete resection in a single session in 86% (18/21) of patients. Patients with lesions extending to more than two thirds of the duodenal circumference required additional sessions for complete resection (2 patients required 2 sessions and 1 required 3 sessions)[2].

The case series of 14 patients reported that all 9 patients treated with ESD were resected en-bloc and that 5 of the 6 patients treated with EMR were resected en-bloc[4].

The case series of 3 patients treated with EMR reported that all lesions were resected with clear margins[6].

### Survival and local recurrence

The case series of 27 patients treated with EMR reported follow-up on only 1 patient who had both a complete resection and high-grade dysplasia (this formed part of a survival analysis of all patients treated in the entire gastrointestinal tract in this study). This patient was still alive at 45 months with no recurrence[1].

A case series of 23 patients (21 treated with EMR) reported that there were no local recurrences in the 8 lesions removed en bloc with EMR at a median follow-up of 13 months. In the same time period, of the 13 lesions removed piecemeal, 5 had remnant adenoma (39% [5/13] of piecemeal resections; 25% [5/20] of all resections available for follow-up). All were treated successfully with snare resection and argon plasma coagulation (APC)(3) or with APC alone (2) and were recurrence-free at median follow-up of 10 months[2].

A case series which included 13 patients with malignant duodenal lesions treated with EMR, 2 by polypectomy and 2 by open surgery reported that there were no deaths or recurrences at a mean follow-up of 51.7 months[3].

A case series of 4 patients treated with ESD reported that all patients were alive with no local recurrences at a mean follow-up of 18 months[5].

A case series of 3 patients treated with EMR reported no recurrences during the mean follow-up period of 21.5 months (the mean follow-up period relates to all patients in the case series including patients with ESD of other GI organ lesions)[6].

## *Safety*

### Perforation

The case series of 14 patients reported perforation in 2 of the 9 patients treated with ESD: one occurred during ESD and was successfully treated with endoscopic clips and the other was a delayed case of bleeding that required surgical treatment (time of delayed perforation not reported). No patients treated with EMR had perforation[4].

In a case series of 4 patients treated with ESD, perforation occurred in 2 patients. The study reported that these were resolved with close postoperative observation including antibiotics and the use of a nasogastric tube (no other details provided)[5].

### Bleeding

In the case series of 27 patients treated with EMR, 33% (9/27) developed bleeding, but further details were only provided for the group of 22 patients who developed bleeding as part of the whole study series (of patients treated by EMR in several GI organs (n = 92). Of these 22 patients with bleeding, 73% (16/22) were reported within 24 hours of EMR and 27% (6/22) had delayed bleeding (after 24 hours). Endoscopic treatment involving clip placement, ligation with a snare or electrocoagulation was performed to treat the bleeding in 88% (14/16) and 33% (2/6) respectively. In addition, 14% (3/22) of patients required blood transfusions (outcomes were not described by indication)[1].

The case series of 23 patients reported that 1 patient with bleeding within 48 hours of EMR was successfully treated with endoscopic clips[2].

The case series including 13 patients with malignant duodenal lesions treated by EMR reported that 1 patient had local bleeding after treatment, which was successfully treated with endoscopic clips[3].

The case series of 14 patients reported postoperative bleeding in 2 of 9 patients treated with ESD and 1 of 5 patients treated with EMR. These were all successfully treated with endoscopic clips[4].

The case series of 4 patients reported that endoscopic clips were used to manage and prevent bleeding in 1 patient treated with ESD[5].

### *Validity and generalisability of the studies*

- There are only very small case series on these procedures for non-ampullary duodenal lesions, which probably reflects its rarity.
- The longest mean follow-up is 51.7 months.
- Only some of the studies were clear about whether patients were diagnosed before they were treated.
- While 4 of the 6 studies in the overview included patients from Japan[3,4,5,6], 2 of the larger case series[1,2] and another small case series[6] included patients from Australia and the USA.
- 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*

#### Interventional procedures

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

## 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 Amjid Riaz, Association of Upper Gastrointestinal Surgeons for Great Britain and Ireland, Dr Bjorn Rembacken, British Society of Gastroenterology.

- One of the Advisers performs this procedure regularly and the other has never performed the procedure but is involved in referring patients for this procedure.

- Theoretical adverse events include delayed haemorrhage, perforation, bleeding, inadequate resection and pain.
- Risk of perforation and bleeding are greater than for the same endoscopic procedure elsewhere.
- Key efficacy outcomes include complete removal rate, recurrence rate, recovery period, morbidity and mortality.
- One Adviser commented that it is difficult to determine recurrence rates in patients with familial adenomatous polyposis because of the potential for the presence of other polyps being incorrectly mistaken for recurrence. There is no recognized training programme for endoscopic removal of lesions from this location. Most train in the technique in the colon first. It is important to have accessible facilities for angiographic embolisation of a bleeding artery, emergency biliary surgery, transfusion services and intensive therapy unit.
- Both safety and efficacy are uncertain but the alternative therapy (Whipple procedure) is a difficult procedure with a recognised high morbidity and mortality rate. Duodenotomy also has a high local recurrence rate.

## Patient Commentators' opinions

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

## Issues for consideration by IPAC

- None

.

# References

1. Ahmad NA, Kochman ML, Long WB et al. (2002) Efficacy, safety, and clinical outcomes of endoscopic mucosal resection: A study of 101 cases. Gastrointestinal Endoscopy 55:390–6.

2. Alexander S, Bourke MJ, Williams SJ at al. (2009) EMR of large, sessile, sporadic nonampullary duodenal adenomas: technical aspects and long-term outcome (with videos). Gastrointestinal Endoscopy 69:66–73.

3. Oka S, Tanaka S, Nagata S et al. (2003) Clinicopathologic features and endoscopic resection of early primary nonampullary duodenal carcinoma. Journal of Clinical Gastroenterology 37:381–5.

4. Honda T, Yamamoto H, Osawa H et al. (2009) Endoscopic submucosal dissection for superficial duodenal neoplasms. Digestive Endoscopy 21:270–4.

5. Takahashi T, Ando T, Kabeshima Y et al. (2009) Borderline cases between benignancy and malignancy of the duodenum diagnosed successfully by endoscopic submucosal dissection. Scandinavian Journal of Gastroenterology 44:1377–83.

6. Waxman I, Saitoh Y, Raju GS et al. (2002) High-frequency probe EUS-assisted endoscopic mucosal resection: A therapeutic strategy for submucosal tumors of the GI tract. Gastrointestinal Endoscopy 55:44–9.

# Appendix A: Additional papers on endoscopic mucosal resection and endoscopic submucosal dissection of non-ampullary duodenal 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 |
|---|---|---|---|
| Coriat R, Mozer-Bernardeau M, Terris B et al. (2008) Endoscopic resection of a large Brunner's gland hamartoma. Gastroenterologie Clinique et Biologique 32:4. | Case report<br>n = 1 benign tumour | A large tumour (6 cm x 54 cm) treated successfully with endoscopic resection. | Larger studies are included in table 2. |
| Doi K, Tada S, Fujimoto T et al. (2004) Successful endoscopic removal of a duodenal adenoma occurring in Brunner's gland hyperplasia. Digestive Endoscopy 16:148–51. | Case report<br>n = 1 duodenal adenoma | Successful removal of Brunner's gland hyperplasia with EMR. | Larger studies are included in table 2. |
| Morita T, Tamura S, Yokoyama Y et al. (2007) Endoscopic resection of a duodenal gangliocytic paraganglioma. Digestive Diseases & Sciences 52:1400–4. | Case report<br>n = 1 gangliocytic paraganglioma treated with EMR | Description of resection by EMR. | 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 = 1 (2 early oesophageal squamous cell, 51 gastric, 17 rectal)<br>Follow-up = 14.4 months | Both were resected en bloc with ESD - 30 mm diameter of resection each.<br>No recurrence or complications in those treated for oesophageal lesions. | Larger studies are included in table 2. |
| Pungpapong S, Woodward TA, Wallace MB et al. (2006) EUS-assisted EMR of a large duodenal carcinoid tumor. Gastrointestinal Endoscopy 63:703–4. | Case report<br>n = 1 with duodenal cardinoid tumour<br>Follow-up = 2 years | Lesion successfully removed with clear margins with EMR.<br>No recurrence at 2 years. | Larger studies are included in table 2. |
| Rosch T, Sarbia M, Schumacher B et al. (2004) Attempted | Case report<br>n = 1 with submucosal duodenal tumour | The lesions was completely resected with ESD and histologically | Larger studies are included in table 2. |

| | | | |
|---|---|---|---|
| endoscopic en bloc resection of mucosal and submucosal tumors using insulated-tip knives: a pilot series. Endoscopy 36:788–801. | (among 37 for entire GI) | shown to be a lipoma. | |
| Sanomura M, Tanaka S, Ito M et al. (2003) Depressed-type, early duodenal carcinoma (carcinoma in situ) treated by endoscopic mucosal resection. Journal of Gastroenterology 38:813–5. | Case report<br>n = 1with early duodenal carcinoma in situ.<br>Follow-up = 1year | Lesion was successfully removed with carcinoma-free margins.<br>No recurrences after 1 year. | Larger studies are included in table 2. |
| Yoshida S, Shimada M, Ueno T et al. (2008) Successful endoscopic submucosal dissection of duodenal cancer. Endoscopy 40: Suppl-3. | Case report<br>n = 1 with early duodenal cancer.<br>Follow-up = 3 years. | Patient successfully treated with ESD. Bleeding during procedure was managed with thrombin, snare coagulation and some endoscopic clips.<br>No recurrence in over 3 years. | Larger studies are included in table 2. |

# Appendix B: Related NICE guidance for endoscopic mucosal resection and endoscopic submucosal dissection of non-ampullary duodenal lesions

| Guidance | Recommendations |
|---|---|
| Interventional procedures | **Endoscopic submucosal dissection of lower gastrointestinal lesions. NICE interventional procedures guidance 335 (2010)**<br><br>1.1 Current evidence on endoscopic submucosal dissection (ESD) of lower gastrointestinal lesions shows that it is efficacious, but evidence on long-term survival when used to treat malignant lesions is limited in quantity. There are some concerns about safety with regard to the risk of perforation and bleeding. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research.<br>1.2 Clinicians wishing to undertake ESD of lower gastrointestinal lesions should take the following actions.<br>• Inform the clinical governance leads in their Trusts.<br>• Ensure that patients understand the uncertainty about the procedure's safety and efficacy in relation to the risks of perforation and bleeding, and that conversion to open surgery may be necessary. Patients should be provided with clear written information. In addition, the use of NICE's information for patients ('Understanding NICE guidance') is recommended (available from www.nice.org.uk/IPG335publicinfo).<br>• Audit and review clinical outcomes of all patients having ESD of lower gastrointestinal lesions (see section 3.1).<br>1.3 Endoscopic submucosal dissection of lower gastrointestinal lesions is a technically challenging procedure and should only be carried out by clinicians with specific training in the technique. The Joint Advisory Group on Gastrointestinal Endoscopy intends to prepare training standards on this procedure.<br>1.4 Patient selection should be carried out either by a colorectal surgeon or by both a colorectal surgeon and an endoscopist who are experienced in this technique.<br>1.5 NICE encourages further research into ESD of lower gastrointestinal lesions. There should be clear documentation of the incidence of complications including perforation, haemorrhage and need for open surgery (with the reasons for this), rates of complete resection, and long-term outcomes including local recurrence and survival.<br><br>**Provisional recommendations for 'Endoscopic submucosal dissection for oesophageal dysplasia and neoplasia' (IP775) (this was discussed at March IPAC and may be removed from this** |

| | |
|---|---|
| | **overview before publication).**<br>1.1 For oesophageal adenocarcinoma or high grade dysplasia in Barrett's oesophagus current evidence on the efficacy of endoscopic submucosal dissection (ESD) is limited in quantity and there is a safety concern regarding the risk of oesophageal perforation. Therefore, in patients with diagnosis of oesophageal adenocarcinoma or high grade dysplasia (HGD) in Barrett's oesophagus this procedure should only be used in the context of research.<br>1.2 For oesophageal squamous carcinoma or dysplasia the current evidence on the efficacy of ESD is limited. This evidence is mostly from Japan where the epidemiology of oesophageal cancer is different to the UK. There are safety concerns – specifically about the risk of oesophageal perforation. Therefore in patients with squamous oesophageal carcinoma or dysplasia this procedure should only be used with special arrangements for clinical governance, consent and audit or research.<br>1.3 Clinicians wishing to undertake ESD for oesophageal squamous carcinoma or dysplasia should take the following actions:<br>• Inform the clinical governance leads in their Trusts.<br>• Ensure that patients and their carers understand the uncertainty about the procedure's safety and efficacy and provide them with clear written information. In addition, the use of NICE's information for patients ('Understanding NICE guidance') is recommended (available from www.nice.org.uk/IPGXXXpublicinfo). [[details to be completed at publication]]<br>• Audit and review clinical outcomes of all patients having ESD for oesophageal squamous carcinoma or dysplasia (see section 3.1).<br>1.4 Patient selection should be carried out by an upper gastrointestinal cancer multidisciplinary team.<br>1.5 ESD for oesophageal dysplasia and neoplasia is a technically challenging procedure and should be carried out only by clinicians with adequate specific training in the technique.<br>1.6 NICE encourages further research into ESD for oesophageal dysplasia and neoplasia. Studies should define clearly the type, grade and stage of cancers or dysplasias being treated. Efficacy outcomes should include adequacy of resection and local recurrence: safety outcomes should include perforations, strictures and their consequences. |

# Appendix C: Literature search for endoscopic mucosal resection and endoscopic submucosal dissection of non-ampullary duodenal lesions

| 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) | 18/12/2009 | Issue 4, 2009 |
| MEDLINE (Ovid) | 15/12/2009 | 19/05/2010 |
| MEDLINE In-Process (Ovid) | 15/12/2009 | 19/05/2010 |
| EMBASE (Ovid) | 18/12/2009 | 19/05/2010 |
| CINAHL (NLH Search 2.0 or EBSCOhost) | 19/05/2010 | N/A |
| BLIC (Dialog DataStar) | 19/05/2010 | N/A |
| National Institute for Health Research Clinical Research Network Coordinating Centre (NIHR CRN CC) Portfolio Database | 18/12/2009 | None found. |
| Current Controlled Trials *meta*Register of Controlled Trials - *m*RCT | 18/12/2009 | Effects of Oral Rabeprazole on the Prevention of Ulcer Bleeding Following Endoscopic Mucosal Resection<br><br>Transanal Endoscopic Microsurgery Versus Endoscopic Submucosal Dissection For Large Rectal Adenomas |
| Clinicaltrials.gov | 18/12/2009 | Endoscopic Mucosal Resection (EMR) for Diagnosis of Hirschsprung's Disease<br><br>Endoscopic Mucosal Resection (EMR) in Barrett's Esophagus<br><br>H. Pylori Eradication on Healing of Iatrogenic Gastric Ulcer by Endoscopic Mucosal Resection |

| | | |
|---|---|---|
| | | Evaluation of Blood as a Submucosal Cushion During Endoscopic Polypectomy and Mucosal Resection |
| Zetoc | 19/05/2010 | N/A |

Websites searched on 18/12/2009

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

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

| | |
|---|---|
| 1 | endoscopy/ or exp endoscopy, digestive system/ or exp endoscopy, gastrointestinal/ |
| 2 | endoscop*.tw. |
| 3 | duodenscop*.tw. |
| 4 | (endoscop* adj3 gastrointest*).tw. |
| 5 | Endoscopes/ |
| 6 | or/1-5 |
| 7 | submucos*.tw. |
| 8 | Intestinal mucosa/ |
| 9 | 7 or 8 |
| 10 | exp Dissection/ |
| 11 | (dissect* or resect*).tw. |
| 12 | microdissect*.tw. |
| 13 | or/10-12 |
| 14 | 6 and 9 and 13 |
| 15 | ESD.tw. |
| 16 | EMR.tw. |
| 17 | 14 or 15 |
| 18 | 14 or 16 |
| 19 | ((gastric* or stomach* or duodenal* or duodenum*) adj3 (ulcer* or lesion* or adenoma* or polyp* or dysplas*)).tw. |

| | |
|---|---|
| 20 | Stomach Ulcer/ |
| 21 | Duodenal Ulcer/ |
| 22 | Intestinal Polyps/ |
| 23 | Gastric Ulcer/ |
| 24 | Precancerous Conditions/ |
| 25 | (precancer* or pre-cancer* or pre-malign* or premalign* or preneoplast* or pre-neoplastic*).tw. |
| 26 | ((early or flat*) adj3 (neoplasm* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan*)).tw. |
| 27 | 24 or 25 or 26 |
| 28 | (stomach* or gastric* or duodenal* or duodenum*).tw. |
| 29 | 27 and 28 |
| 30 | (neoplasm$ or cancer$ or carcinoma$ or adenocarcinom$ or tumour$ or tumor$ or malignan$).tw. |
| 31 | Stomach Neoplasms/ |
| 32 | Duodenal Neoplasms/ |
| 33 | Intestinal Neoplasms/ |
| 34 | 28 and 30 |
| 35 | 19 or 20 or 21 or 22 or 23 or 29 or 31 or 32 or 33 or 34 |
| 36 | 35 and 17 |
| 37 | 35 and 18 |
| 38 | limit 36 to english language |
| 39 | limit 37 to english language |
| 40 | 1999*.ed. |
| 41 | 2000*.ed. |
| 42 | 2001*.ed. |
| 43 | 2002*.ed. |
| 44 | 2003*.ed. |
| 45 | 2004*.ed. |
| 46 | 2005*.ed. |
| 47 | 2006*.ed. |
| 48 | 2007*.ed. |
| 49 | 2008*.ed. |
| 50 | 2009*.ed. |

| | |
|---|---|
| 51 | or / 40-50 |
| 52 | 38 and 51 |
| 53 | 38 and 51 |
| 54 | 50 or 46 or 47 or 48 or 45 or 49 |
| 55 | 39 and 54 |
| 56 | 38 and 54 |