

## Endoscopic removal or ablation of oesophageal and gastric superficial tumours

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### Abstract

Endoscopic mucosal resection was developed in Eastern countries as a curative treatment for superficial carcinomas in the stomach and oesophagus. Experience in Western countries is more recent and limited due to less frequent diagnosis of early gastric cancers compared to the Japanese and Korean populations and to more frequent use of ablation techniques such as argon plasma coagulation and photodynamic therapy in pre-neoplastic lesions and superficial tumours. This review summarizes the respective indications, advantages, disadvantages, limitations and complications of the different ablative and resection techniques in the upper gastrointestinal tract. Several methods are described such as electrocoagulation, argon plasma coagulation, photodynamic therapy, lift and cut resection, cap assisted aspiration and band ligation mucosectomy, and endoscopic submucosal dissection. Local results in more than 170 patients managed with endoscopic resection of oesophageal high grade dysplasia or squamous cell carcinoma and gastric or Barrett's epithelium high grade dysplasia or adenocarcinoma furthermore demonstrate the safety and effectiveness of endoscopic resection practiced in experienced centres. (*Acta gastroenterol. belg.*, 2006, 69, 304-311).

### Introduction

Endoscopic mucosal resection (EMR) was developed in Eastern countries such as Japan and Korea as a curative treatment for superficial carcinomas in the stomach and oesophagus. In a 1984 publication, Tada *et al.* for the first time described the use of 'strip-off biopsy' as a treatment option in early gastric carcinoma (1). This was the start of the gradual acceptance of ER as a therapeutic and diagnostic procedure in the upper gastrointestinal tract. The first ER procedures for early oesophageal carcinoma were carried out in the early 1990s, again by Japanese endoscopists (2,3). It was only several years later that the first Western research groups published their experience in ER for oesophageal neoplasia (4,5). The reasons may be a less frequent diagnosis of early cancers and a more frequent use of ablation techniques such as argon plasma coagulation (APC) and photodynamic therapy (PDT).

Endoscopic treatment of superficial upper GI tumours may be divided into resection and ablation techniques. Resection remains the gold standard management because it provides a pathological specimen that will be stage the lesion. Resection is however time consuming when aimed at large lesions or in difficult areas of the digestive tract (6). The terms of "EMR" or "mucosectomy" are in fact inappropriate since resection includes a part of the submucosa. They should therefore be replaced by the term "endoscopic resection" (ER).

Different techniques have been developed for piece-meal or "en-bloc" resection such as cap assisted resection, band ligation, or more recently endoscopic submucosal dissection (ESD) and full thickness resection, which is also useful as a diagnostic procedure by obtaining a full-thickness mucosal specimen for histological examination.

Ablation provides an alternative for resection and has been particularly studied in Barrett's high grade dysplasia in which large surfaces need sometimes to be treated and in which the risk of metastatic lymph nodes remains exceptional when tumours are limited to the mucosa.

These techniques will be described in this review with their respective indications, advantages, disadvantages, limitations and complications. The discussion will focus on local results of endoscopic resection of squamous cell carcinoma or high grade dysplasia and high grade dysplasia or adenocarcinoma developing in gastric or Barrett's epithelium.

### Endoscopic resection techniques

Various ER techniques have been described (7). The techniques more commonly used are the strip biopsy (8); the inject and cut (9); the inject, lift, and cut; the simple suction and snare (4); the cap-assisted endoscopic mucosal resection (3); and the endoscopic mucosal resection with ligation (10,11).

#### *The lifting techniques*

<i>Advantages :</i>	– <i>easy to perform</i> – <i>cheap procedure</i>
<i>Disadvantages :</i>	– <i>risk of perforation (if no injection)</i> – <i>specimen size limitations</i> – <i>piece-meal resection for large tumours</i>
<i>Indications :</i>	– <i>polypoid lesions (type I, IIa)</i> – <i>Barrett's mucosa</i>
<i>Complications :</i>	– <i>perforation</i> – <i>bleeding</i>

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In strip biopsy, a diathermy loop is introduced through the working channel of the endoscope and positioned over a polypoid lesion, which is fixed by tightening of the loop and slowly detached using electrical cutting current (8). This technique can be used in polypoid tumours (type 1), but with flat lesions it is difficult to position the loop, and there may be a risk that the size of the removed specimen will be limited. Nevertheless, this technique has been advocated and has been successfully used in the resection of flat early Barrett's carcinomas (4). Submucosal injection of a solution can lift flat or depressed lesions (type II) and make it easier to resect them (the 'lift-and-cut' technique). The type of injection solution used has not been standardized. The solution most often used is saline with epinephrine or dextrose in various concentrations (6).

#### The suction techniques

<b>Advantages :</b>	– safe in the oesophagus (more risks of perforation in hiatal hernia or stomach), – easy and fast when operator is experienced
<b>Disadvantages :</b>	– piece-meal for large tumours – risk of perforation if the tumour is attached to the muscularis propria (post-ulcer fibrosis or malignant infiltration), – costly when multiples snares are used
<b>Indications :</b>	– especially indicated in the oesophagus for flat tumours or pre-neoplastic lesions – small gastric mucosal lesions – removal of small submucosal tumours
<b>Complications :</b>	– perforations (exceptional) – bleeding (rare) – oesophageal strictures when (near)-circumferential resection is attempted

The 'suck-and-cut' technique is used in the oesophagus worldwide and more frequently than the strip biopsy, due to the anatomical conditions. In the stomach endoscopic suck-and-cut mucosectomy was found more effective in early gastric cancer than the strip biopsy with regard to the largest diameter of the resected specimen, the rate of en-bloc resection, and the complication rate (12).

In the early nineties, Inoue *et al.* developed the cap technique, thereby improving the effectiveness of ER in comparison with simple strip biopsy (13). In the ER cap technique, a specially developed transparent plastic cap is attached to the end of the endoscope. After injection under the target lesion, the lesion is sucked into the cap and resected with a diathermy loop that has previously

been loaded onto a specially designed groove on the lower edge of the cap. Since injecting underneath early carcinomas often makes it difficult to distinguish them, prior marking of the lesion e.g., using electrocautery is recommended. The suck and ligation resection is another mucosectomy technique in which a ligation device is used, either single use or reusable, single band or "variceal" multiple band loaded (14,15). In this method, the target lesion is sucked into the ligation cylinder, and a polyp is created by releasing a rubber band around it. The polyp is then resected at its base, either above or below the rubber band, using a diathermy loop. Similar results were observed between cap and ligation techniques in removal of oesophageal mucosal lesions (16).

#### ER with needle-knife techniques

<b>Advantages :</b>	– "en-bloc" resection – resection of poorly lifting lesions
<b>Disadvantages :</b>	– more expertise is needed – risk of perforation is increased – costly if several knives are used – substantial time required – difficult technique in the oesophagus
<b>Indications :</b>	– (large) superficial tumours in the stomach (type II a-b-c)
<b>Complications :</b>	– bleeding (frequent, needs appropriate haemostatic tools) – perforation

Endoscopic submucosal dissection (ESD) technique is a new endoscopic method using cutting devices, which remove the lesion by the following three steps: injection of fluid into the submucosa to elevate the lesion from the muscle layer, pre-cut of the surrounding mucosa of the lesion, and dissection of the connective tissue of the submucosa beneath the lesion (17). The major advantages of this technique in comparison with conventional EMR are: first, the resected size and shape can be controlled, second, en bloc resection is possible even in a large lesion, and third, the lesions with ulcerative findings are also resectable. Nowadays, several knives for ESD such as a needle knife (18, 19), an insulated-tipped (IT) knife (20), a hook-knife (21), a triangle-tipped (TT) knife (22), and a flex-knife (23) are available for ESD. In the largest prospective study so far published on this technique, en-bloc removal was achieved in 89% of the lesions if the lesions did not exceed 20 mm in diameter. From the point of view of tumour pathology, en-bloc resection is certainly the ideal procedure (24-26).

In the stomach, low risk tumours theoretically considered as good indications for ESD are as follows (27):

– Mucosal carcinoma:

Differentiated adenocarcinoma, irrespective of ulcer findings, < 3 cm in diameter,

Differentiated adenocarcinoma, without ulcer findings, > 3 cm in diameter

Undifferentiated adenocarcinoma, without ulcer findings, < 2 cm in diameter

– Submucosal carcinoma with minute submucosal penetration :

Differentiated adenocarcinoma, < 500 µm below the muscularis mucosa, < 3 cm in diameter

However, preoperative prediction of the fulfilment of the above criteria is not possible in all the lesions, so that ESD can also be considered to obtain a histological evaluable en-bloc specimen (28). The indication of ESD should be discussed in a multidisciplinary team and may depend on local expertise, according to the technical achievements, determined by each institution or each operator (29).

However, substantial time is required to complete the resection and practical issues arise in the oesophagus, therefore limiting its applicability in Western countries where Barrett's tumours are more frequent than mucosal gastric cancers.

### Ablative therapies

<i>Advantages :</i>	<ul style="list-style-type: none"> <li>– <i>PDT can treat large areas</i></li> <li>– <i>APC and MPEC : easy and cheap technique</i></li> <li>– <i>less invasive than EMR or ESD</i></li> <li>– <i>potential advantages of APC compared with MPEC include ease of use (no contact coagulation) and limited depth of tissue penetration</i></li> </ul>
<i>Disadvantages :</i>	<ul style="list-style-type: none"> <li>– <i>no pathological specimen</i></li> <li>– <i>depth of coagulation uncertain</i></li> <li>– <i>risk of residual submucosal intestinal metaplasia</i></li> <li>– <i>risk of intramucosal adenocarcinoma arising under neosquamous epithelium</i></li> <li>– <i>PDT : risk of stricture, high cost</i></li> </ul>
<i>Indications :</i>	<ul style="list-style-type: none"> <li>– <i>multifocal HGD in Barrett's oesophagus</i></li> <li>– <i>combination therapy with other local endoscopic resection techniques</i></li> </ul>

Ablative endoscopic treatment options include electrocoagulation by means of argon plasma coagulation, multipolar electrocoagulation (MPEC), heat probe, laser therapy (neodymium-yttrium aluminium garnet (Nd:YAG) laser ablation (30)), cryotherapy (31), photodynamic therapy and recently balloon-based radiofrequency energy ablation (32). APC and MPEC have been most commonly applied, perhaps because they are most readily available in GI endoscopy units and result in relatively superficial injury with few major complications. At least 12 independent centres have evaluated APC in

444 patients with Barrett's oesophagus, making this far and away the most commonly performed thermal technique (33).

In Barrett's epithelium, the foundational principles are controlled damage to the Barrett's mucosa followed by healing in an anacid environment, provided by high dose proton pump inhibitors. This results in neopithelium that appears to be normal squamous mucosa in the majority of patients. The average thickness of Barrett's epithelium is 0.5 mm (34). The average thickness of Barrett's mucosa is 1.5 mm, and oesophageal-wall thickness is at its greatest distally at 4 mm by EUS (35). Depth of injury reported in the literature varies considerably for each ablative technique. The depth of MPEC is between 1.7 to 4.8 mm, depending on watt setting, degree of pressure applied to the probe, and duration of application (36). Photodynamic therapy is reported to have a depth of 1 to 2 mm but seems inconsistent with the high-stricture rate that exceeds that of MPEC or APC. Sampliner reports that depth of injury generally follows this pattern : PDT and Nd:Yag > MPEC > argon laser (36).

Residual subsquamous intestinal mucosa after ablation of Barrett's oesophagus is of unknown significance and is reported to occur with all ablation modalities (33). Of concern is the rare development of intramucosal adenocarcinoma arising under neosquamous epithelium after ablation, despite apparent macroscopic and microscopic clearance of Barrett's oesophagus (37). In a most recent study of post-PDT Barrett's oesophagus patients, 51.5% had subsquamous intestinal mucosa (38).

Combination therapy with other local endoscopic procedures appears to be useful and justifiable in individual cases. If evidence of minimal residual carcinoma at the resection margin is found after ER, ablation of the residual tissue using APC can be useful. In patients with multifocal intraepithelial high-grade neoplasia, extensive ablation using PDT is indicated as a supplement to ER in individual cases.

#### *Argon plasma beam coagulation (APC)*

APC is a form of monopolar, no contact, and thermal-coagulation therapy. A plasma of charged argon gas expelled from the tip of the APC probe conducts an electrical current from a dedicated electrosurgical generator to nondesiccated tissue. As vital tissue undergoes coagulative necrosis, it becomes desiccated. Electrical resistance increases, interrupting conduction, thereby halting further tissue injury. This concept allows relative reliability and reproducibility of depth of tissue injury, i.e., coagulative necrosis. Compared with endoscopic laser therapy, most commonly with an Nd:YAG laser, for ablation of EGC, APC similarly is applied via a no contact mode that allows rapid "painting" of large surface areas. However, APC facilitates a more uniform treatment effect and enables en face as well as oblique application. Because of the electrosurgical principles it

obeys, the risk of perforation is less with APC compared with Nd :YAG. Also, APC systems are considerably less expensive to acquire and maintain compared with establishing and maintaining a laser capability. For all these reasons, APC has largely replaced ELT for virtually all applications of endoscopic no contact thermal ablation therapy.

### PDT

The principle of PDT is selective sensitization of pre-cancerous or malignant lesions when using a systemically applicable photosensitizer with subsequent, endoscopically controlled, photo chemically induced tissue ablation (39). Hematoporphyrin derivative, a photosensitizer with more side effects, such as post therapeutic stenosis or prolonged photosensitivity of the skin for several weeks initially was used ; but, in recent years, 5-aminolevulinic acid (ALA)-induced protoporphyrin IX (5-ALA-PpIX) has been used in clinical practice (40). The main advantages of 5-ALA-PpIX are that its phototoxic side effects are only minimal and that there is a well-tolerated local reaction of the mucosa, with selective destruction of the mucosa that does not induce strictures.

Compared with ER, the major disadvantage of PDT is that the procedure does not provide a specimen that can be processed histopathologically to assess tumour-free margins and infiltration depth. The major advantage of PDT, in comparison with other endoscopic therapies, is that the method makes it possible to ablate a large circumferential area of neoplastic mucosa by using a specially designed "through-the-scope" PDT balloon, up to a length of 8 cm in a single treatment session (41). Therefore, PDT seems to be the superior endoscopic treatment method for patients with multifocal or widespread Barrett's neoplasia, but, randomized prospective studies to compare PDT, e.g., with ER, are needed to answer this question.

### Local results with ER

Since January 2000, 170 patients have been treated by endoscopic resection of tumours of the upper GI tract, at our institution, including 108 oesophageal, 25 gastric, and 37 duodenal tumours. We use almost exclusively the "suck-and-cut technique" in the oesophagus (Fig. 1) (Barrett's epithelium cases and squamous cell carcinoma), ESD in the stomach and cap assisted (Fig. 2) or lift-and-cut resection in the duodenum. APC is sometimes used for remnant islets of Barrett's epithelium. The injection solution is a mixture of saline, epinephrine diluted at 1:100 000, methylene blue and methylhydroxypropylcellulose (Artelac®) 1:10 in the oesophagus and 1:3 in the stomach. Patients are staged by endoscopy (size, type of lesion) and EUS (radial or linear array PENTAX echoendoscopes EG-3630-UR or EG-3830-UT, connected to a Hitachi EUB6500 and/or 20 MHz miniprobes).

### Oesophageal tumours

108 consecutive patients (mean age 67 y, range 47-88, sex ratio 84M/24F) with (pre)malignant oesophageal tumours of oesophagus, staged as T1 m1-m2-sm1-sm2, N0 by conventional endosonography and 20 MHz miniprobes, were treated with ER after submucosal injection. Outcome was compared between low (lesion type I, IIa, IIb less than 20 mm or IIc less than 10 mm, stage m or Tis, well or moderately differentiated) versus high risk patients classified pre-operatively according to Ell *et al.* (42). 60 patients were classified as low risk group and 48 as high risk. The lesions were squamous cell carcinoma, adenocarcinoma and high grade dysplasia in Barrett's oesophagus in 31, 35 and 42 patients, respectively. 469 ER specimens were removed in 1.3 (range 1-3) treatment sessions per patient, with a mean of 4.0 ER pieces per mucosectomy (range 1-15). Mean follow-up is now 22.2 months (range 1-70). Low risk group significantly differed from high risk group when considering recurrence during follow up (3.3% vs. 29.1%,  $P < 0.05$ ), regardless of histological type of tumour. Complications occurred in 14% of sessions and included 1 perforation successfully closed by endoscopic clipping and 13 oesophageal strictures requiring 1-11 endoscopic dilatations and stenting in 3 patients. During follow-up 3 patients died of various diseases not related to their oesophageal cancer and one patient died of cachexia and pneumonia after a long course of oesophageal stricture needing stenting and complicated by a pleural fistula. Fourteen patients in the high risk were further referred for surgical resection or complementary chemo- or radiotherapy.

With a rate of 97% radical complete resection, ER may be considered as a highly effective and safe method of endoscopic treatment for superficial malignant oesophageal tumours classified as low risk. ER in high risk lesions should only be undertaken in patients unfit for surgery or as a staging procedure. Outcome after ER indeed depends not only on proper staging of patients before treatment, but also on the lecture of the pathology specimen obtained by ER. This allows adequate patients' selection for further surgery or radio chemotherapy.

### Full resection of Barrett's epithelium with high grade dysplasia or mucosal cancer

Full resection of Barrett's oesophagus with high grade dysplasia or T1m N0 adenocarcinoma staged by radial or linear EUS was performed in 27 patients, starting at the site of the tumour, after submucosal injection of 2-5 ml aliquots of a saline solution described above for a total of 10-50 ml, than resecting the remaining Barrett's mucosa from distal to proximal direction, in 1 to 3 sessions. Oblique or straight transparent rigid or soft cap was used and resection was completed, if necessary, by APC (0.6 L, 60 W) for residual bridging or short remaining tongs of metaplasia. Patients were discharged

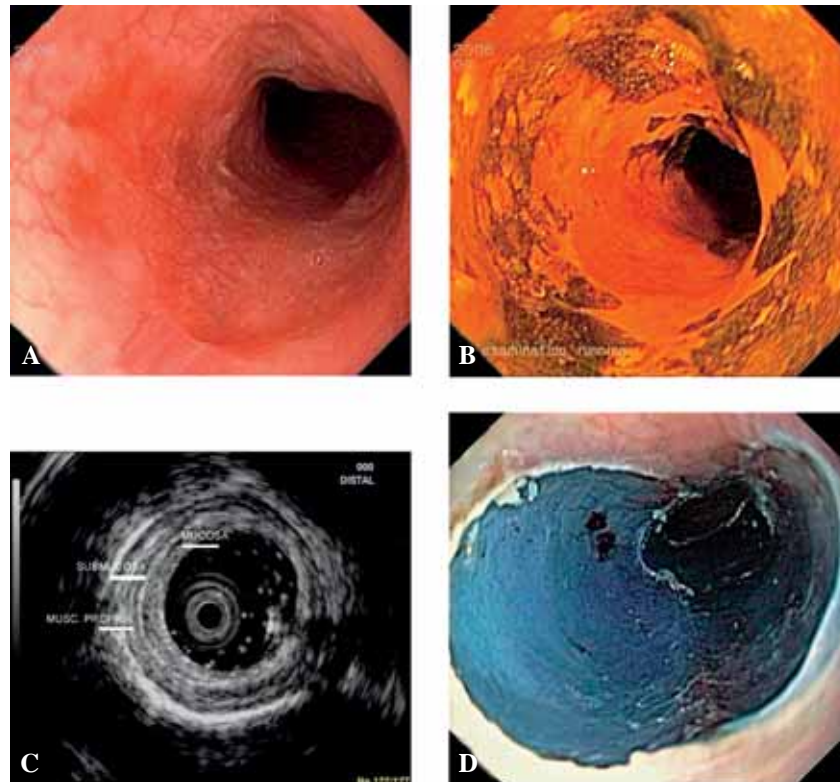


Fig. 1. — Endoscopic resection by cap aspiration technique of squamous cell carcinoma in mid-oesophagus  
 A : endoscopic view of a tumour type IIb ; B : chromoendoscopy with lugol 2% staining ; C : endosonography with 20 MHz miniprbes showing thickening of the mucosa without extension to the submucosa ; D : after peace-meal (n = 3 specimen) resection of 75% of the circumference, leaving a bridge of intact mucosa.

one or two days after mucosectomy under liquid diet and omeprazole 40mg bid was started before treatment and continued for 8 weeks minimum. Mean age of the patients was 68 y, range 47-85, 3 women/24 men and they presented with HGD in 19 and intramucosal adenocarcinoma in 8, respectively. Mean circumferential length of Barrett's mucosa (Prague C) was 19 mm (range 5-70 mm) and mean highest limit (Prague M) was 28 mm (range 5-80 mm). A total of 47 ER sessions were performed (1.3 ; 1-5), removing 156 specimens (5.7 ; 1-13 per patient). Follow-up is now 25.3 months (1-72 months). Successful resection of HGD and adenocarcinoma was observed in all but one patient (97%). Complete removal of intestinal metaplasia was observed in 65% of patients, with 2 patients still presenting low grade dysplasia. Remaining Barrett's mucosa was however limited to sections of < 5 mm in all patients. Three patients presented recurrence of HGD at the "neo" gastroesophageal junction and were successfully treated by ER or APC. Oesophageal stenosis was observed in 9 patients (33%) more frequently when entire circumferential resection was attempted in only one ER session. Balloon dilatation (1-6 sessions) was successful in all patients (1-6 sessions) except one who was treated with a plastic expandable stent.

#### *Gastric mucosal lesions : ER and ESD*

Twenty five patients presenting gastric tumours were considered for endoscopic treatment when EUS (radial scanning or 20 MHz miniprbes) staged the lesions as T1mN0. ER was performed using the cap method in 17 patients (smaller lesions and early experience) and by ESD in 8 cases. Resection involved peripheral marking with needle knife, APC or Flex-knife, submucosal injection and either cap aspiration or submucosal dissection with Flex-knife, Hook-knife, and IT-knife. Complete remission was defined as the absence of adenocarcinoma or high grade dysplasia at the last follow-up examination. Histological diagnosis on the resected specimen revealed tubulo(villous) adenoma with low grade dysplasia in 6 cases, high grade dysplasia in 12 patients, mucosal adenocarcinoma in 5 patients, submucosal adenocarcinoma in 1 and diffuse type adenocarcinoma in 1. Complete remission was obtained in 22/25 patients, with a median follow-up of 26 months. The 3 patients with incomplete resection (submucosal adenocarcinoma, persistent HGD and diffuse type adenocarcinoma) were referred for elective surgery. During the early period of the study (before 2004), 3 patients with HGD or intramucosal cancer treated by ER underwent subsequent

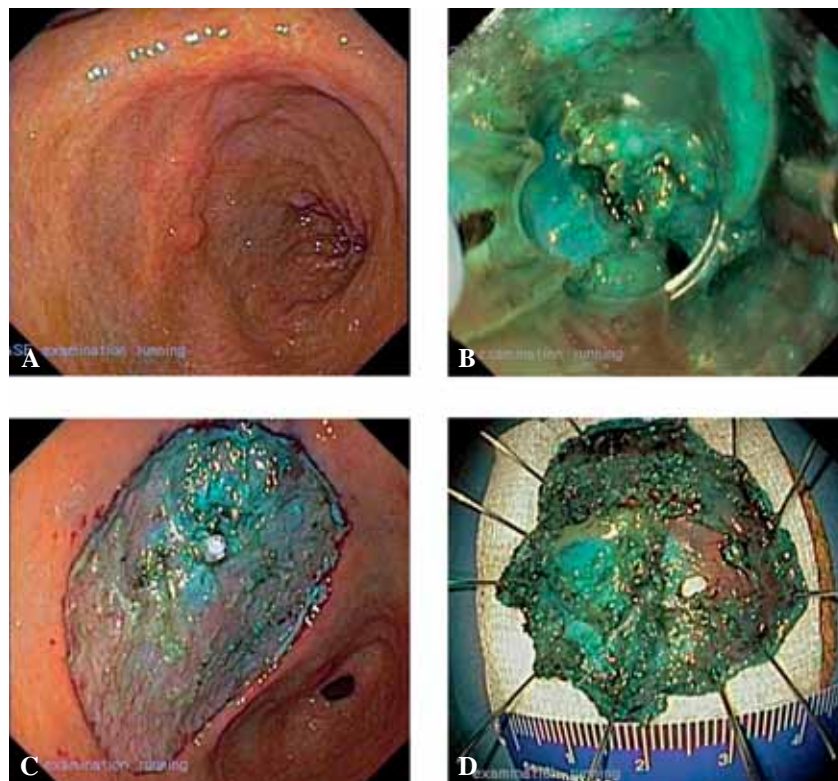


Fig. 2. — Endoscopic submucosal dissection and resection of a type IIa lesion with mucosal (pT1m3) adenocarcinoma  
 A : superficial antral gastric tumour type IIa ; B : dissection with a transparent hood and Flex-knife® ; C : after resection, large area of nude submucosa ; D : the 4 cm wide specimen is placed on a cork + wet mesh with submucosa on top.

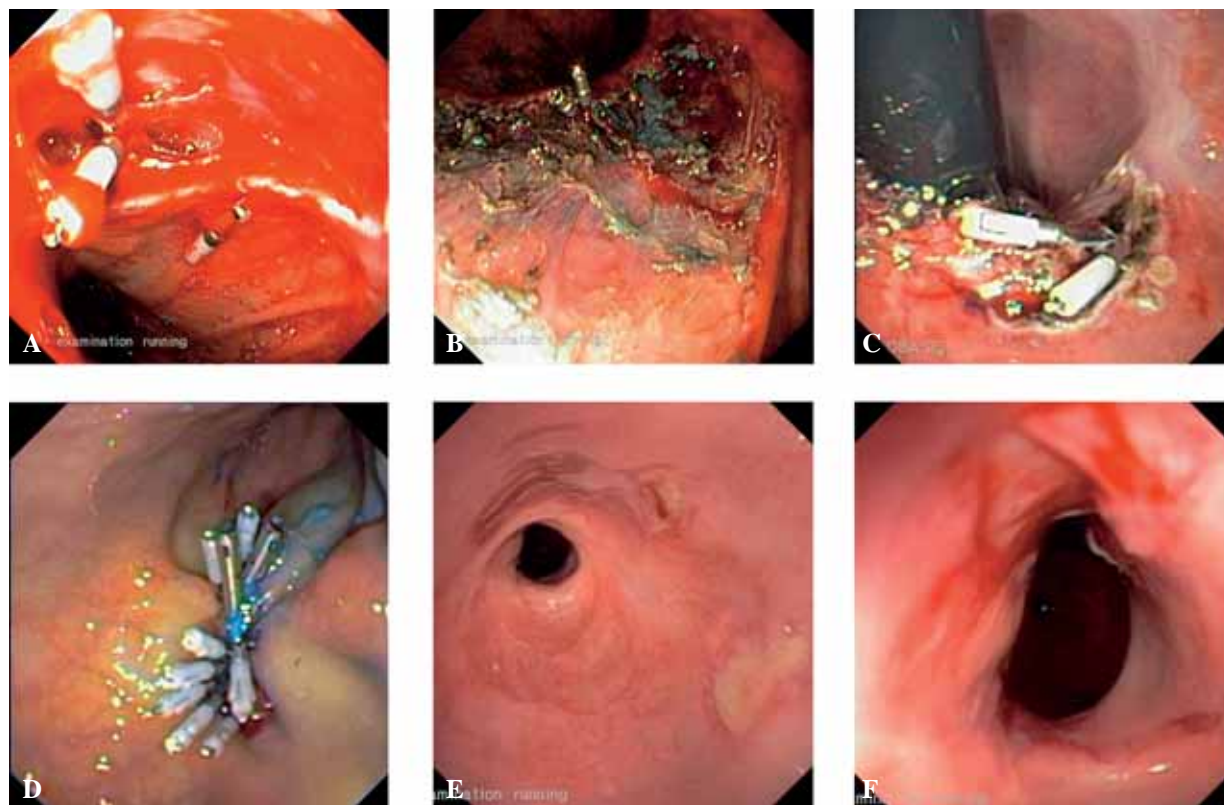


Fig. 3. — Various complications and their endoscopic treatment  
 A+B : active bleeding and haemoclips ; C : clipping in retrograde position in a hiatal hernia ; D : gastric perforation closed by application of 11 clips ; E + F : lower oesophagus stricture after Barrett's HGD resection, before and after dilation with 18 mm balloon.

surgery because of uncertain deep or lateral margins : none of the surgical specimen harboured residual tumour. Strict endoscopic follow-up might therefore be the preferred attitude in these cases. Complications were limited to one perforation successfully managed by endoscopic clipping. Intraoperative bleeding was not considered as a complication and was treated by coagulation (20/25) or hemocliping (14/25) successfully in all patients (Fig. 3).

## Conclusions

### General statements

*Prior to endoscopic therapy, precise staging of an early oesophageal (pre-) malignancy at an experienced centre is mandatory.*

*The 'suck-and cut' technique should be used for ER in the oesophagus.*

*High-grade intraepithelial neoplasia and mucosal carcinoma in Barrett's oesophagus should be treated endoscopically with a curative intent.*

*Endoscopic therapy of early neoplastic lesions in Barrett's should only be performed in experienced centres*

### Current indications for ER

#### Oesophagus

- Well and/or moderately differentiated squamous cell carcinoma confined to the lamina propria with no evidence of venous or lymphatic involvement. The risks of lymph-node metastases in cancer limited to the epithelium and involving the lamina propria are approximately 0% and 3%, respectively (43). These risks increase rapidly to 12% and 26% with deeper cancers involving the muscularis mucosa and the upper third of the submucosal layer, respectively
- There is no consensus on the maximal size although circumferential lesions are usually avoided because of potentials for stricture formation.

#### Stomach

- Mucosal carcinoma :
  - Differentiated adenocarcinoma, irrespective of ulcer findings, < 3 cm in diameter,
  - Differentiated adenocarcinoma, without ulcer findings, > 3 cm in diameter
  - Undifferentiated adenocarcinoma, without ulcer findings, < 2 cm in diameter
- Submucosal carcinoma with minute submucosal penetration :
  - Differentiated adenocarcinoma, < 500 µm below the muscularis mucosa, < 3 cm in diameter without evidence of venous or lymphatic involvement.

The risk of lymph node metastases has been reported to be practically nonexistent in differentiated cancers less than 20 mm, without ulceration or involvement of the lymphatic or venous vessels (44). Type IIc mucosal cancers less than 10 mm have practically no risk of lymph-node involvement, whereas those with type IIc less than 20 mm have a 0.4% risk. The risk of lymph-node metastasis, however, increases rapidly for submucosal invasive cancers (24). In general, EMR is not indicated for undifferentiated (poorly differentiated adenocarcinoma and/or signet-ring cell carcinoma) type, even for small lesions, because of a significant risk of lymph-node involvement (26).

In experienced hands, ER is a safe method of resecting dysplastic lesions and early carcinomas, and it has decisive advantages in comparison with other local endoscopic treatment procedures (such as thermal destruction and PDT) : the opportunity for histological processing of the resected specimen provides information regarding the depth of invasion of the individual layers of the gastrointestinal tract wall, and regarding radicality of the resection. Moreover, this strategy implies that even when there appears to be infiltration of the submucosa that has not been detected before treatment e in which case local endoscopic therapy is no longer appropriate e this patient is still able to undergo surgical resection.

Curative endoscopic treatment of early oesophageal carcinomas should only be carried out in centres with a sufficient. Randomized controlled studies comparing radical oesophagectomy or new function-preserving operations (29) with endoscopic therapy are desirable, but they are difficult to conduct because valid 5-year survival data are now available showing no significant difference between patients who have undergone endoscopic treatment for early cancers and the average population of the same age and sex.

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