Endoscopic eradication of Barrett's oesophagus with early neoplasia
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CHAPTER 1

Endoscopic resection of early oesophageal and gastric neoplasia

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ABSTRACT

The last decades, endoscopic treatment of early neoplastic lesions in oesophagus and stomach has evolved as a valid and less invasive alternative to surgical resection. Endoscopic resection (ER) is the cornerstone of endoscopic therapy. Next to the curative potential of ER, by removing neoplastic lesions, ER may also serve as a diagnostic tool. The relatively large tissue specimens obtained with ER enable accurate histological staging of a lesion, allowing for optimal decision making for further patient management. ER was pioneered in Japan, mainly for the resection of gastric lesions and squamous oesophageal neoplasia, and also Western countries have been increasingly implementing ER in the treatment of early gastro-oesophageal neoplasia, mostly associated with Barrett’s oesophagus. In this review we will give an overview of different techniques that have been developed and modified for ER of early gastro-oesophageal neoplasia, and we will discuss the indications for ER in the oesophagus and stomach.

INTRODUCTION

The last two decades endoscopic therapy has been proven a safe and effective alternative to surgery for the treatment of early gastro-oesophageal neoplasia. The cornerstone of endoscopic therapy is endoscopic resection (ER), which is not only a potential curative tool, but may also serve as an excellent diagnostic aid. ER was pioneered in Japan, mainly to resect early gastric cancers and early squamous lesions in the oesophagus. Also in Western countries endoscopic treatment has gained acceptance and has increasingly been implemented, mostly for the management of early neoplasia associated with Barrett’s oesophagus (BO). In contrast to surgical resection, which also allows for dissection of local lymph nodes, ER is limited to local removal of a lesion. Only patients with a minimal risk of lymph node metastases are, therefore, candidates for curative endoscopic treatment. This implies that optimal selection of patients for ER is of the utmost importance. Lesions limited to the mucosa (i.e. m1-m3) have a minimal risk of lymphatic involvement and may be treated endoscopically. Lesions infiltrating deep into the submucosa, poorly differentiated cancer, or the presence of lymphatic/vascular invasion are considered risk factors for lymph node metastasis and are, therefore, indications for surgical treatment. Next to detailed endoscopic inspection of a lesion and assessment of the infiltration depth with endoscopic ultrasound, the optimal staging tool is a diagnostic ER that provides a relatively large tissue specimen for accurate histological evaluation of these risk factors, on which further patient management can be based. A wide range of different ER techniques and tools have been developed and modified to facilitate ER, make the procedure safer, and to allow for removal of neoplasia in one piece. In this chapter we will discuss different ER techniques, novel developments in this area, and indications for ER in the oesophagus and stomach.

GENERAL ASPECTS OF ENDOSCOPIC RESECTION

En-bloc resection vs. piecemeal endoscopic resection

Most conventional ER techniques allow for en-bloc resection of lesions with a maximum diameter of 2 cm. Larger lesions require resection in multiple resections during a so-called “piecemeal” procedure. Piecemeal resections are technically more demanding, time-consuming, have a higher risk of complications, and are associated with a higher rate of local recurrence. In addition, piecemeal resections go against the basic principles of oncology, since histological evaluation of the radicality of a resection is not reliable. En-bloc resection is, therefore, preferable and should always be aimed at.

Delineation and marking of the target lesion

To ensure radical resection of a suspicious lesion with a disease free margin, it is important to delineate the extent of a lesion with detailed endoscopic inspection using a high-quality endoscope. Advanced imaging techniques, such as chromoendoscopy (e.g. using acetic acid, indigo carmine, Lugol staining), zoom-endoscopy or narrow-band imaging may be helpful to assess the extent of a lesion. Since the endoscopic view during ER may be impaired by the use of distal attachment caps, submucosal lifting and bleeding, it is advisable to place coagulation markings 2-5 mm outside the lateral margins of the target lesion. The markings can be made with an argon plasma coagulation (APC) probe, the tip of an elec-
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Chapter 1

Part I - Endoscopic Resection

Submucosal lifting

For some ER techniques, the mucosa needs to be lifted from the deeper wall layers by injection of a fluid into the submucosal layer. This submucosal lifting makes the mucosa more accessible for resection and it protects the deeper oesophageal wall layers from thermal injury and perforation. Furthermore, the type of submucosal lifting may provide useful information on the infiltration depth of a lesion. Kato et al. described four types of submucosal lifting in relation to the infiltration depth in a series of colorectal cancers. Type I lifting was described as complete, soft lifting that made the lesion stretch like a ‘dome’, and these lesions only showed superficial infiltration (max. T1sm1) upon histological evaluation. With type II lifting the lesion lifted completely, but hard, meaning that the form of the lesion was maintained. Lesions with type II lifting were mostly mucosal lesions, some were T1sm2, but all lesions could be resected radically. When the lesion could be lifted, but stayed behind compared to the surrounding mucosa (type III lifting), this was associated with submucosal infiltration, mostly T1sm2. If there was no lifting at all (type IV lifting), most colorectal lesions penetrated deep into the submucosa (T1sm3). Type IV lifting is, therefore, a contraindication for ER. In BO and in the stomach, however, it has to be noted that prior ulceration and inflammation may have resulted in scarring that impairs submucosal lifting.

Endoscopic Resection Techniques

Strip-biopsy ER

The strip-biopsy was the first technique described in relation to ER. For strip-biopsy a double-channel endoscope is used. After submucosal lifting of the target area, a polypectomy snare is opened over the lesion, and through the second working channel of the endoscope a grasping forceps is introduced to pull the mucosa through the opening of the snare. By pushing the snare down and closing it, the mucosa is captured in the snare and can be resected using electrocautery. Since the strip-biopsy technique does not require the use of a distal attachment cap visualization of the target lesion is optimal, and the centre of the lesion can be targeted precisely with the grasping forceps. By grasping the lesion, however, the tissue is damaged, impairing the histological evaluation, and the specimens obtained with strip-biopsy are usually small (10-15 mm) resulting in a low rate of radical en-bloc resections. In addition, strip-biopsy requires the use of a double-channel endoscope and an additional assistant. A number of different modifications to the strip-biopsy technique have been reported. For the resection of protruding lesions the double-snare strip-biopsy technique has been described, where a second snare is used for grasping the mucosa instead of a grasping forceps. Inoue et al. were the first to report on the use of a transparent overtube to provide better visualization of the lesion, decrease the risk of perforation, to make grasping of the lesion easier by suctioning the lesion into the tube, and to enable manipulation of the lesion to a better position. Another strip-biopsy modification described placement of 4 clips around the lesion, to enable easy and correct positioning of the snare around the lesion.

For resection of lesions that are difficult to approach, ER using a side-viewing endoscope, a special electrocautery snare, and a partial transparent cap has been reported. None of these modifications on the strip-biopsy technique are, however, widely used nowadays.

Lift-and-snare technique (Fig. 1)

With the lift-and-snare technique the target area is first marked, then lifted with submucosal fluid injection and subsequently resected by closing a polypectomy snare directly over the elevated lesion. The most commonly used snares for this technique are normal braided polypectomy snares. The braided, round wires of these snares have little friction with the mucosa, and since these snares are often relatively soft, the tip of the snare may lift off the mucosa when the proximal end is pressed against the mucosa during closure. To avoid the lesion to slip out of the snare during closure, it is important to correctly position the opened snare and to apply suction while closing the snare. To make capturing of lesions easier, special snares are available, for example snares with a short needle at the tip, to allow it to be anchored into the mucosa, to hold it from being lifted off when the proximal end of the snare is being pushed down. Other snares have small hooks attached to the wires on both sides of the loop to increase friction with the mucosa. Furthermore, stiff monofilament snares with a rectangular shape are available. The relative stiffness prohibits the distal tip of the snare from lifting up during snare closure, and the “sharper” edges make it easier to grasp the lesion. For flat type lesions or lesions in difficult locations, however, it remains difficult to capture the lesion and to achieve targeted, complete en-bloc resection. In the upper GI-tract, the lift-and-snare technique is mainly used in the stomach. For oesophageal lesions the lift-and-snare technique is, however, often not preferable, since most lesions in the oesophagus are located tangentially to the endoscope making positioning of the snare difficult. Giovannini et al. have used this technique for widespread mucosal resections in squamous and Barrett’s oesophagus using a needle-tipped polypectomy snare.

Simple snare technique

The simple snare, or bare snare, technique is comparable to the lift-and-snare technique, but without the submucosal lifting. The snare is simply placed over the target area and pressed against the mucosa that is drawn in the loop by applying suction via the endoscope. The snare is then closed and the mucosa is resected using electrocautery. For en-bloc resection of a lesion the simple snare technique may be less suitable, since it is difficult to position the centre of the lesion in the snare, and keep it there during closure of the snare. For resection of flat mucosa without focal lesions, however, the simple snare technique can be useful. The Hamburg-group has used a monofilament snare with a diameter of 0.4 mm, measuring 30x50 mm when opened, for widespread oesophageal ER, and despite the lack of submucosal lifting they did not encounter any perforations.
PART I - Endoscopic Resection

Endoscopic resection of lesions with a maximum diameter up to 2 cm.14 A drawback of the ER-cap technique is that areas that are difficult to reach with other techniques, such as the lesser curvature of the stomach or the dorsal wall of the antrum, are readily accessible using the lift-and-snare technique. In addition, resection specimens obtained with the ER-cap technique are easier to obtain, and resect the mucosa, single use crescent shaped snares with a small tip are used. Because the snare does not break, the ER-cap technique is that it is a technically demanding and time consuming procedure, especially when used for piecemeal resections. Prelooping the snare in the distal rim of the cap can be challenging, and for piecemeal resections submucosal lifting needs to be repeated for every resection. For the ER-cap technique a number of different attachment caps are available that fit on most standard and therapeutic endoscopes. The choice ranges from hard caps, either straight or oblique shaped, with an outer diameter of 12.8-16.1 mm to flexible oblique caps with an outer diameter of 18 mm. The oblique caps are best suited for lesions that are located tangentially to the endoscope (such as in the oesophagus), whereas straight caps can be used for lesions that are approached en face. The large calibre flexible cap results in larger and deeper resections, which increases the chance of resecting a lesion en-bloc. For piecemeal resections, however, using the large calibre cap may increase the risk of complications, such as perforation. The use of standard hard caps may, therefore, be advisable for piecemeal resections. To capture submucosal fluid injection, and then a crescent shaped snare is prelooped in the distal rim of the cap. The lifted mucosa is approached with the endoscope, suctioned into the cap, and by ligating the mucosa the pseudo-polyp is created. This pseudo-polyp can then be resected with a snare. For the ligate-and-cut technique a number of different accessories are available. The multi-band mucosectomy device (Duette®, Wilson Cook, Limerick, Ireland) consists of a transparent cap that holds six rubber bands and allows for passage of a 7 Fr hexagonal snare through the accessory channel of the cranking device alongside the releasing wires, allowing resection after ligation without having to remove the endoscope.34,35 The re-usable Euroligator device (Euroligator; Mandel and Rupp, Erkrath, Germany) consists of a non-transparent cap that only holds one rubber band, and after ligation of the mucosa the endoscope needs to be removed in order to introduce a snare to resect the pseudo-polyp.36 An advantage of the ligate-and-cut technique over the lift-suck-and-cut technique is that no submucosal lifting is required, since the rubber band is not strong enough to hold in the deeper oesophageal wall layers. This makes the ligate-and-cut technique easier and quicker to apply, especially when used for piecemeal procedures.37 Despite the lack of submucosal lifting, the ligate-and-suck technique does not appear to be associated with a higher risk of complications as has been demonstrated in studies comparing both techniques.35-37

Ligate-and-cut technique (Fig. 3)

The ligate-and-cut technique is an easier alternative to the lift-suck-and-cut technique. For the ligate-and-cut technique a distal attachment cap, holding one or more rubber bands, is attached to the tip of the endoscope. The target lesion is sucked into the cap and by releasing a rubber band the mucosa is captured. This pseudo-polyp can then be resected with a snare. After APC markings are placed around the lateral margins of the lesion. F: After submucosal lifting, an electrocautery snare is prelooped in a distal rim in the ER-cap, and the lesion is targeted. G: The ligate-and-cut technique over the lift-suck-and-cut technique is that no submucosal lifting is required, since the rubber band is not strong enough to hold in the deeper oesophageal wall layers. This makes the ligate-and-cut technique easier and quicker to apply, especially when used for piecemeal procedures.37 Despite the lack of submucosal lifting, the ligate-and-suck technique does not appear to be associated with a higher risk of complications as has been demonstrated in studies comparing both techniques.35-37

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Endoscopic submucosal dissection (ESD) is a technique that overcomes the problem of piecemeal ER for larger neoplastic lesions, and allows for a better-targeted resection of a lesion. By using ESD the indication for ER is, therefore, extended to lesions with a diameter $\geq 2$ cm. The concept of ESD is to incise the mucosa around a lesion, regardless how large, and then remove the mucosa by submucosal dissection using an electrosurgical knife instead of a snare. After careful delineation of a lesion, coagulation markings can be placed around the lesion using the tip of an electrosurgical knife, about 5 mm outside the margins of the lesion. The marked incision line and the mucosa within the markings are lifted by submucosal fluid injection. With an electrosurgical knife, the incision line can then be incised circumferentially around the lesion, while constantly repeating submucosal lifting to ensure a safe submucosal fluid cushion. When the incision around the lesion has been completed, the submucosa underneath the lesion can be dissected completely to remove the diseased part of the mucosa in one piece. A range of different techniques and types of electrosurgical instruments have been developed, of which the most widely used techniques are described below.

**ESD using an IT knife**

The insulated-tipped knife (IT knife) (KD-610L, Olympus, Tokyo, Japan) has a tip that is insulated with a small ceramic ball that prevents injury to the muscularis mucosa while dissecting the mucosa and submucosa.$^{38-41}$ After submucosal lifting, a small mucosal incision is made with a standard needle knife, through which the ceramic ball of the IT knife can be introduced. The rest of the needle knife can then be used to make the circumferential mucosal incision, and subsequently to dissect the submucosa. Since the tip of the IT knife cannot be used for the dissection, all the cutting has to be performed with the blade that only allows for limited direction of the cutting.

**ESD using a hook knife**

The hook knife (KD-620LR, Olympus, Tokyo, Japan) has a ‘hooked’ tip of 1 mm in length that can be rotated to the optimal cutting direction.$^{41}$ The hook of the knife can be used to hook onto the submucosal tissue, pull it, and then cut it, which allows for safe resection. If a transparent ESD cap is used, the tissue can be pulled into the cap, making resection even safer.

**ESD using a flex knife**

The flex knife (KD-630LR, Olympus, Tokyo, Japan) is a spiralled, multi-filament snare with a round tip and a flexible soft sheet. The flex knife can be adjusted in length and can be used to place markings, to make the initial circumferential incision, and to perform the submucosal dissection.$^{41,42}$

**ESD using an ST hood**

The small-calibre-tip transparent hood (ST hood) (DH15GR, Fujinon, Saitama, Japan) can be placed on the tip of an endoscope and is used to open the incision line for better visualization of the submucosal layer during the submucosal dissection, making the procedure easier and safer.$^{43}$ It can be used in conjunction with any of the aforementioned ESD knives.

**ESD using a TT knife**

The triangular tip knife (TT knife) (KD-640L, Olympus, Tokyo, Japan) has a small triangular metal tip that can be used for multiple purposes during ESD.$^{44}$ The tip can be used to place markings, to perform the mucosal incision around the lesion, and to dissect the submucosa. The plate of the triangular tip allows for effective coagulation of blood vessels.

**Novel developments and experimental techniques for ER**

**Use of novel endoscopes**

To facilitate ESD, new double-bending endoscopes have been developed that allow for optimal positioning of the endoscope during the procedure. Next to the normal up-down and left-right bending possibilities at the distal end of a normal GI-endoscope, the double bending endoscope has a proximal bending section that allows for up- and downward deflection to optimally position the endoscope during ESD.$^{45,47}$ This so-called “R-scope” (XGIF−2TQ240R, Olympus, Tokyo, Japan) also has two working channels making it possible to insert a grasping forceps through one channel that allows vertical movement to lift the mucosa up and away from the muscle layer. An electrocautery knife can be inserted through the second working channel that allows for horizontal movement to dissect through the submucosa. In a small-sized study, ESD using the “R-scope” showed to be equally effective as conventional ESD in expert hands, but the mean operating time was significantly shorter in “R-scope” procedures.$^{44}$ For endoscopists with less experience in performing ESD, the
R-scope facilitated ESD in porcine models, and a small series of human cases. A drawback of the R-scope, however, is its relatively large diameter of 14.3 mm resulting from the incorporation of two movable instrument channels and the multibending system, which makes working in the retroflex position difficult. Further refinements of this therapeutic “R-scope”, however, may make it a useful tool for ESD.

**Use of a water-jet for submucosal lifting and dissection**

A novel development that allows for easy and effective submucosal lifting is the use of the Helix HydroJet (Erbe Elektromedizin GmbH, Tübingen, Germany). The HydroJet can produce a focused water jet that may be used for dissection of interstitial tissue and parenchymatous organs. The precise water jet is able to separate parenchyma, while it leaves fibrous tissue, such as vascular walls and nerve tissue, unharmed. Studies in porcine models and in human oesophagectomy specimens have demonstrated that the HydroJet can successfully penetrate the mucosa to create a selective fluid accumulation in the submucosal layer. The use of HydroJet submucosal lifting for the ER and ESD has to be evaluated in clinical studies, but due to its selective dissecting properties it appears to optimize and facilitate the procedures.

**Use of balloon-assisted techniques**

Another development that may allow for safer and easier endoscopic resection of early neoplasia is the use of balloon-assisted techniques. After submucosal lifting, a mucosal incision is made through which a balloon, e.g. a biliary retrieval balloon catheter, is inserted into the submucosal space. By inflating the balloon, the mucosa is mechanically separated from the deeper wall layers, without the need for electrocautery. By repeated inflation, a marked lesion can be completely loosened from the underlying muscularis propria, and this mucosal flap can then be resected with a needle knife. This approach has, however, only been evaluated in the porcine stomach, but may prove an easy and safe technique for ER in the future, and may overcome the problem of electrocautery artifacts that may impair histological evaluation.

**INDICATIONS FOR ENDOSCOPIC RESECTION**

**Early neoplasia arising in Barrett’s oesophagus**

Endoscopic resection for early neoplasia in BO has been proven safe and effective for lesions limited to the mucosa (m1-m3). The risk on lymph node metastasis in these patients is <2%, which is lower than the 30-day mortality risk after surgical oesophagectomy. Indications for ER in a BO are solitary lesions type 0-I, 0-IIa, 0-IIb or type 0-IIc, with a maximum diameter of 2 cm. If histopathological evaluation shows that a lesion was radically resected, limited to the mucosa (HGNI, m1, m2, m3), and if there were no signs of lymphatic or vascular infiltration, it can be assumed that the patient was curatively treated. In these patients additional treatment to eradicate the residual Barrett’s epithelium to prevent metachronous lesions is justified. Relative indications for ER of early Barrett’s neoplasia are infiltration in the superficial submucosa (T1sm1, <500 µm), poorly differentiated cancer (G3), and lesions with a diameter >2 cm. Treatment of these patients should be performed at expert centres, or under an IRB-approved study protocol. In case of infiltration beyond the superficial submucosa (>sm1), lymphatic or vascular infiltration, or undifferentiated cancer (G4), patients should not be treated endoscopically, but with alternative treatment modalities such as surgery, chemo- and/or radiotherapy.

**Early neoplasia arising in the squamous oesophagus**

Compared to Barrett’s neoplasia, ESCC invades the muscularis mucosae and submucosa at a particularly early stage, lymphatic invasion then occurs quickly, and distant metastases are seen in nearly 30% of patients. Indications to perform ER of ESCC are flat type lesions (type 0-Ila, 0-IIb, 0-IIc) that are mostly limited to the mucosa. Protruding (0-II) and ulcerated lesions (type 0-IIII) almost always invade the submucosa and should not be resected endoscopically. Lesions that are histologically confined to the epithelium and lamina propria (m1, m2) have a very low rate of local lymph node metastases (<5%) and are considered amenable for endoscopic treatment. Lesions invading into the muscularis mucosa (m3) or superficial submucosa (sm1), however, have an increased risk of lymph node metastases of approximately 10%. These lesions are, therefore, only relative indications for endoscopic treatment, e.g. in patients who carry an increased risk for severe complications of oesophagectomy.

**Early gastric neoplasia**

In 2001 the Japanese Gastric Cancer Association first published the “Gastric Cancer Treatment Guidelines”. According to these guidelines, ER is indicated for lesions with a negligible risk of lymph node metastases, defined as: well to moderately differentiated lesions with a maximum diameter <2 cm, no signs of ulceration, and without submucosal infiltration or lymphatic/vascular invasion in the ER specimen. The restriction for the size of the lesion, <2 cm, is based on the assumption that with conventional ER techniques only lesions up to 2 cm can be removed en-bloc. Larger lesions require piecemeal ER, which makes assessment of the radicality of the resection impossible and which has an increased risk of residual neoplasia or local recurrence. With the use of ESD, however, the indications for ER of early gastric neoplasia have widened since ESD allows for en-bloc resection of lesions >2 cm. The indications for ER have been extended in the guidelines reported in 2004 that also indicate ER/ESD for: 1) well to moderately differentiated mucosal cancer, without ulceration, irrespective of its size. 2) well to moderately differentiated mucosal cancer, with or without ulceration, <3 cm. 3) poorly differentiated mucosal cancer, without ulceration, <2 cm. In addition, the guidelines state that additional lymph node resection is not necessary when lymphatic and/or vascular invasion is absent and when the tumour is limited to the superficial submucosa (T1sm1, <500 µm). The endoscopic treatment can, however, only be regarded as curative in case the resection specimen shows a radically resected well/moderately differentiated cancer without lymphatic/vascular invasion, limited to the mucosal layer.
FUTURE PROSPECTS OF ENDOSCOPIC RESECTION

For early neoplasia arising in Barrett’s oesophagus promising new ablation techniques, such as radiofrequency ablation (RFA), will adopt an important position in endoscopic treatment. For early neoplasia arising in Barrett’s oesophagus promising new ablation techniques, such as radiofrequency ablation (RFA), will adopt an important position in endoscopic treatment. RFA has been proven safe and effective in the eradication of Barrett’s epithelium and its associated dysplasia. Although ER will remain essential to remove visible lesions for diagnostic purposes and to render the mucosa flat, RFA may make widespread resections in BO unnecessary. Also for early squamous neoplasia, focal ER of visible lesions followed by RFA of residual flat type dysplasia may be a promising treatment modality. For other indications that still require widespread ER, techniques that allow for en-bloc resection, such as radiofrequency ablation (RFA), will adopt an important position in endoscopic treatment.

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SUMMARY

Over the last decades, ER of early gastro-oesophageal neoplasia in selected patients has been proven a safe and effective alternative to surgical resection. Adequate endoscopic work-up to identify patients that are eligible for endoscopic treatment is of the utmost importance, to select patients with a minimal risk of lymphatic involvement that can be cured by local endoscopic treatment. ER plays a pivotal role in this patient selection since it provides a large tissue specimen for accurate histological evaluation of risk factors for lymphatic involvement. To ensure optimal endoscopic work-up, histological evaluation and patient management, patients should be referred to centres with multidisciplinary expertise in this field. A number of different ER techniques are available. Developments such as the multi-band mucosectomy device make widespread ER easier, faster and possibly safer. Other developments, such as ESD, widen the indication for ER by allowing en-bloc resection of lesions with a diameter >2 cm. A number of promising new techniques are being developed all aimed at making ER easier to perform, safer, and to allow for en-bloc resection of larger lesions.

REFERENCES


