Endoscopic eradication of Barrett's oesophagus with early neoplasia
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Citation for published version (APA):

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Endoscopic treatment has evolved as a valid and less invasive alternative to surgery in patients with early neoplasia in Barrett’s oesophagus (BO). Treatment protocols are constantly being improved based on results from ongoing research in this field, and technical developments in endoscopic imaging, resection and ablation. Endoscopic resection (ER) is the cornerstone of endoscopic therapy, allowing for curative removal of neoplasia and accurate histological staging. To prevent recurrences in the remainder of the Barrett’s segment after focal ER of neoplasia, it is advocated to eradicate all intestinal metaplasia. To achieve this, different approaches, such as stepwise radical ER and radiofrequency ablation (RFA), have been studied. This thesis contains a number of studies that have added greatly to the current management of patients with early Barrett’s neoplasia. Below, we have summarized the most important findings from these studies.

The first part of this thesis is focused on ER. Chapter 1 contains a review on different techniques that have been developed and modified for ER of early neoplasia in the upper gastro-intestinal tract. Furthermore, indications for ER in the oesophagus and stomach are discussed.

During work-up prior to endoscopic treatment, endoscopic ultrasound (EUS) is often used for locoregional staging of early oesophageal neoplasia. However, its value next to endoscopic inspection and diagnostic ER may be questioned, since diagnostic ER allows for histological assessment of submucosal invasion, and other risk factors for lymph node metastasis, e.g. poor differentiation and lymph-vascular invasion. Chapter 2 describes a retrospective cohort study on the additional value of EUS during work-up including ER. In this large study in 131 patients with early oesophageal and cardia neoplasia, we found that the additional value of EUS was very limited. In none of the 131 patients EUS alone changed the treatment policy. Furthermore, the results of this study strengthened the role of diagnostic ER as a final step in the work-up for endoscopic treatment.

The most widely used technique for ER of early Barrett’s neoplasia is the ER-cap technique. ER-cap requires submucosal lifting and positioning of a snare in the cap, making it technically demanding and laborious. Multi-band mucosectomy (MBM) is a relatively new ER technique, which uses a modified variceal band ligator and requires no submucosal lifting or positioning of a snare. Chapter 3 describes a multicenter, randomized controlled trial comparing ER-cap and MBM for piecemeal ER of early Barrett’s neoplasia in 84 patients. The study concludes that piecemeal ER with MBM is significantly faster and cheaper than with ER-cap. In addition, MBM appears not to be associated with more perforations despite the lack of submucosal lifting. MBM may thus be preferred for piecemeal ER of early Barrett’s neoplasia.

After focal ER of neoplasia, there is a risk of 30% that patients will develop metachronous lesions in the remainder of their BO. To prevent these recurrences during follow-up, remaining Barrett’s mucosa can be removed by stepwise radical endoscopic resection (SRER). By combining the experience from four European centers to eradicate BO <5 cm
containing early neoplasia by SRER, we were able to include 169 patients, making this the largest and longest followed cohort treated with SRER, described thus far. As reported in Chapter 4, SRER achieved complete eradication of neoplasia and intestinal metaplasia in 97.6% and 85.2% of patients, respectively. After median follow-up of 32 months, complete eradication of neoplasia and intestinal metaplasia was sustained in 95.3% and 80.5% of patients, respectively. However, SRER is technically demanding and was associated with oesophageal stenosis in half of the patients. The stenosis rate was correlated with the length of the resected BO and although we anticipate that SRER may also be successful in patients with BO >5 cm, we feel that this currently is the upper limit for safe and effective SRER.

The second part of this thesis is focused on radiofrequency ablation (RFA). Chapter 5 is a review on stepwise circumferential and focal RFA using the HALO system. The review explains the technical background of RFA and gives a summary of its indications in BO.

The Academic Medical Center in Amsterdam was the first centre worldwide to treat Barrett’s patients with high-grade intraepithelial neoplasia with RFA, as well as to perform RFA after ER for focal neoplasia. Aim of chapter 6 was to report the results of the first 44 patients with early Barrett’s neoplasia treated with RFA at our centre. In 31 patients ER of visible lesions was performed prior to RFA. After ablation, complete histological eradication of all neoplasia and intestinal metaplasia was achieved in 43 patients (98%). Complications following ablation were superficial mucosal laceration at the resection site (n=3) and transient dysphagia (n=4). These first experiences with RFA for treatment of BO containing early neoplasia showed that RFA, with or without prior ER for visible abnormalities, is an effective and safe treatment modality for this indication.

After the promising results of RFA at the Academic Medical Center, we wanted to evaluate if these results could be reproduced in a larger European multicenter setting. We therefore initiated a pilot study in three European centers, including 24 patients (EURO-I study). As described in Chapter 7 RFA, with or without prior ER for visible lesions, achieved eradication of neoplasia and intestinal metaplasia in 95% and 88% of patients, and additional escape ER in 2 patients in 100% and 96%, respectively. Complications after RFA included melena (n=1) and dysphagia (n=1). Furthermore, during the first half of this study, 5 mucosal lacerations were observed within the ER-scar area during circumferential RFA. We related these lacerations to extensive baseline ER and scarring. None of the lacerations required intervention or caused complaints and, therefore, they were regarded as mild complications. However, since lacerations may potentially provoke severe bleeding or oesophageal perforation, the investigator group added a restriction to the baseline extent of ER (max 50% of circumference, 2 cm length), after which no further lacerations were observed. After an additional median follow-up of 22 months no neoplasia recurred. This pilot study, performed in Amsterdam, Düsseldorf and Brussels, demonstrated that early neoplasia in BO can be effectively and safely treated with RFA, in combination with limited ER of visible lesions.

As described previously, our multicenter study on SRER showed that this approach is highly effective in eradication all neoplasia and intestinal metaplasia, however, technically demanding and associated with a high stricture rate. The promising results of RFA, its high safety profile, and relatively easy application, raised the question which approach is superior for treatment of BO <5 cm with early neoplasia. We therefore initiated a randomized controlled trial in three European centers with experience in both SRER and RFA, to compare the safety and efficacy of both techniques. As described in Chapter 8, complete eradication of all neoplasia was achieved in 100% of SRER patients, and in 96% of ER+RFA patients. Complete eradication of all intestinal metaplasia was achieved in 92% of SRER patients, and 96% of ER+RFA patients. Although SRER and ER+RFA achieved comparable high rates of eradication of neoplasia and intestinal metaplasia, SRER was associated with a higher number of complications and therapeutic sessions. For patients with early neoplasia in BO <5 cm, the combined use of focal ER followed by RFA may thus be preferred over SRER.

After the promising results from the European pilot study described in chapter 7, a large-scale European multicenter study was set up in 13 centers with expertise in management of early Barrett’s neoplasia (EURO-II study). For this study, patients with BO measuring up to 12 cm in length were included. These patients were treated by a combination of ER for visible lesions, followed by RFA to eradicate the remainder of the Barrett’s mucosa. Based on the experiences from the first European trial, ER was limited to 2 cm in length and 50% of the circumference. A unique feature of this trial was that all endoscopists participating in this study were trained in RFA at the coordinating site to standardize technique. Furthermore, all RFA procedures as well as the first follow-up endoscopy for each patient were attended on-site by a coordinating study team to ensure protocol compliance. Histological revision was performed at the coordinating study site for all ER-specimens, pre-RFA biopsies, and biopsies from the first follow-up visit. As described in Chapter 9, eradication of intestinal metaplasia and neoplasia was reached in 91% and 96% of patients, respectively. Adverse events during RFA occurred in 10% of patients, all superficial mucosal lacerations at an ER-scar or proximal reflux-stenosis, none requiring additional intervention and therefore all graded as “mild”. This largest prospective multicenter study, with a unique training set-up, and continuous quality control throughout the study period, suggests that RFA plus ER is very effective and safe for treatment of BO containing early neoplasia, when performed by trained, expert endoscopists in carefully selected patients.

After RFA, the neosquamous mucosa appears completely normal upon endoscopic inspection. To evaluate if the neosquamous mucosa is indeed comparable to normal squamous epithelium in the oesophagus, we were the first to study the histological and immunohistochemical properties of neosquamous epithelium that regenerates after RFA, as described in Chapter 10. First, we assessed if RFA is able to erode pre-existing genetic abnormalities in neoplastic BO. For this, we obtained biopsies and brush cytology specimens from the baseline Barrett’s segment and from the post-RFA neosquamous mucosa in 22 patients. These tissue specimens were used for fluorescent in-situ hybridization (FISH) and immunohistochemical staining. We found that all specimens obtained from the pre-treatment BO showed genetic abnormalities, while all post-RFA specimens were normal. Second, we evaluated sampling depth for biopsies obtained from untreated squamous mucosa, and for biopsies from post-RFA neosquamous mucosa. Lamina propria was sampled in 37% of
biopsies obtained post-RFA, which was comparable to the 36% of biopsies from untreated squamous mucosa containing lamina propria. Third, we wanted to assess the presence of buried Barrett’s in post-RFA neosquamous mucosa. For this, we obtained four-quadrant biopsies every 2 cm of neosquamous epithelium. To sample the mucosa even deeper, keyhole biopsies were obtained from each biopsy site. Furthermore, we performed ER of an area of neosquamous mucosa. No buried Barrett’s glands were found in any of the biopsies or keyhole biopsies. Also none of the ER-specimens, all containing submucosal tissue, showed buried glandular mucosa. In summary, the results of our study showed that the genetic abnormalities present at baseline in patients with neoplastic BO are completely absent after RFA. Further, we found that there is no difference in our ability to sample the lamina propria between post-RFA and untreated squamous epithelium, so scarring due to RFA is unlikely. Lastly, we did not detect buried Barrett’s in any post-RFA biopsy using a rigorous assessment with keyhole biopsies and ER. These data therefore suggest that the neosquamous epithelium in patients treated with RFA for BO with neoplasia, may have a reduced risk for malignant transformation and that we are not missing occult buried Barrett’s with our standard post-RFA follow-up biopsy regimen.

All studies in this thesis show that buried Barrett’s after RFA are extremely rare. In our experience, however, biopsies from small residual islands of non-buried Barrett’s mucosa after RFA are occasionally reported to contain “buried Barrett’s” upon histological evaluation, despite the fact that these islands of columnar mucosa were visible endoscopically. In Chapter 11 the frequency of buried Barrett’s in biopsies obtained from small residual Barrett’s islands (<5 mm) sampled post RFA, was compared to biopsies from endoscopically normal neosquamous epithelium. In 2,515 biopsies from endoscopically normal neosquamous epithelium, buried glands were found in 0.1% of biopsies. However, when small islands of columnar mucosa were biopsied, buried glands were detected in 21% of biopsies. This study therefore concludes that to avoid accidental sampling of small islands resulting in a false positive histological diagnosis of buried Barrett’s, thorough inspection should be performed before obtaining biopsies during post-RFA follow-up.