Advances in endoscopic resection and radiofrequency ablation of early esophageal neoplasia
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Summary
SUMMARY

Introduction

This thesis describes recent developments in the endoscopic treatment of early esophageal neoplasia. Endoscopic treatment has replaced surgery as an effective and less invasive strategy for early neoplasia in Barrett’s esophagus (BE). Since patients with BE have an increased risk for the development of esophageal adenocarcinoma, they undergo regular surveillance endoscopies to detect neoplasia at an early stage. Once high-grade dysplasia or early carcinoma is detected, all Barrett’s epithelium (intestinal metaplasia) is at risk for malignant proliferation and needs to be removed. Currently, the preferred endoscopic approach is endoscopic resection (ER) of focal lesions followed by radiofrequency ablation (RFA) of the complete Barrett’s segment.

Part One: Endoscopic Resection

Endoscopic resection of focal lesions is the cornerstone of endoscopic treatment of patients with esophageal high-grade dysplasia or early cancer. ER results in removal of the lesions, and yields a resection specimen for histological staging. ER, however, is a technically demanding procedure, requiring training and expertise, not only to resect lesions in a safe and effective manner, but also to manage potential complications such as bleeding and perforation.

To assess the learning curve of ER, we evaluated the efficacy and safety of the first 120 ER procedures of early esophageal neoplasia in the setting of an intense, structured ER training program (Chapter 1). In 120 ER procedures performed by six participating endoscopists (20 procedures each), complete endoscopic removal of the marked visible lesion was achieved in 93%. The perforation rate was 5%, which was significantly higher than reported in other series from our center. No learning effect was found in this study. All perforations were adequately managed. We concluded that performing 20 endoscopic resections may not have been sufficient to reach the peak of the learning curve in endoscopic resection. The relatively high perforation rate may reflect the complexity of the ER procedure and the consequently long learning curve.

To identify the most important learning points in performing ER during the training program, we assessed written feedback reports of 33 video recordings of unsupervised ER procedures, and asked the six participating endoscopists to complete a questionnaire on their learning points during the training program (Chapter 2). Three endoscopists with experience in ER selected the most important learning points: to ensure and optimize the endoscopic view by choosing the best available endoscope and cleaning of the area of interest; to rotate the endoscope to position the lesion at 6 o’clock; to delineate the lesion by placing electrocoagulation markers hereby creating a ‘preprocedural plan’, and to perform a test-suction prior to every resection to avoid too much overlap or residual tissue bridges. This study resulted in a useful summary of ‘do’s and don’ts in ER’, which may be valuable for endoscopists with an interest in learning or improving ER technique.
In Chapter 3, we compared two different ER techniques for the endoscopic treatment of early esophageal neoplasia in a multicenter randomized trial. The ER-cap technique requires submucosal lifting and positioning of a snare in the cap, making it technically demanding and laborious. The newer multiband mucosectomy technique (MBM) employs a modified variceal band ligator and requires no submucosal lifting or positioning of a snare. In 84 patients who underwent piecemeal ER of Barrett’s neoplasia, no differences in safety and efficacy were found. Despite the lack of submucosal lifting, MBM was not associated with more complications. Importantly, piecemeal ER with MBM was faster and cheaper than with the ER-cap technique. Therefore, MBM is the preferred method for piecemeal ER of early Barrett’s neoplasia.

Part Two: Radiofrequency ablation

RFA treatment results in superficial ablation of the esophageal mucosa of 0.5 to 1 mm in depth, and can be used as a single-modality therapy for flat type dysplasia, or as an adjunct to ER, after ER of visible abnormalities. The technical background of RFA is described in detail in Chapter 4. After initial circumferential ablation with the balloon-based HALO$^{360}$-electrode, focal ablation of residual BE areas and the gastro-esophageal junction is performed with the HALO$^{90}$-electrode. Generally, three ablation sessions with intervals of two to three months suffice to achieve complete eradication of early neoplasia and intestinal metaplasia (IM) in 86-100% and 77-100% of patients, respectively. RFA is associated with a very low rate of stenosis and buried Barrett’s glands as compared to other ablation techniques such as photodynamic therapy and argon plasma coagulation.

Before the introduction of RFA, stepwise radical endoscopic resection (SRER) was the standard endoscopic treatment for early Barrett’s neoplasia. SRER is a technique in which the complete BE segment is removed in consecutive ER sessions with 2-month intervals. The potential advantage of SRER over RFA, is that it results in a complete specimen of the BE segment for histological staging. However, SRER is technically demanding and associated with stenosis. In Chapter 5, we compared SRER versus focal ER followed by RFA for complete eradication of BE containing early neoplasia in a multicenter randomized trial. Forty-seven patients with early neoplasia in BE of ≤5 cm in length were included. Both techniques achieved comparably high success rates, with complete eradication of neoplasia in 100% after SRER and 96% after ER/RFA, and complete eradication of IM in 92% and 96%, respectively. The stenosis rate, however, was significantly higher in SRER patients with 88% versus 14% in ER/RFA patients, resulting in significantly more treatment sessions in SRER patients (6 versus 3) due to subsequently needed dilation sessions. In conclusion, for patients with BE ≤5 cm containing early neoplasia a combined endoscopic approach of focal ER followed by RFA is preferred over SRER.

Once the safety and efficacy of RFA in patients with a BE length up to 8 cm was established in several multicenter trials in the United States and Europe, we aimed to assess the feasibility of RFA for patients with longer Barrett’s segments. In Chapter 6, we described a series of 26 consecutive patients with early neoplasia in BE of minimally
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10 cm in length. This study showed that RFA for longer BE segments may be more challenging, since ablation treatment was stopped in 15% of patients due to poor healing or poor regression, which may reflect the severity of reflux disease in this patient group. Nevertheless, complete eradication of neoplasia and IM was achieved in 83% and 79% of patients respectively, without severe complications and in a similar number of RFA sessions compared to patients with shorter BE segments. This study demonstrated that RFA with or without prior ER is safe and effective for long segment BE.

Given the excellent results of RFA with or without prior ER for early Barrett’s neoplasia, we hypothesized that this approach was also suited for early squamous neoplasia of the esophagus. In Chapter 7, we reported a prospective case series of 13 patients with early squamous neoplasia who were treated with the combined approach of ER followed by RFA. All patients had at least one unstained lesion upon Lugol’s chromoendoscopy containing high-grade dysplasia or mucosal squamous cell cancer. In the case of non-flat lesions, ER was performed for staging and to render the mucosa flat for subsequent RFA. All 13 patients achieved a complete response after a median of two RFA sessions, and there were no recurrences during a median follow-up of 17 months. This study suggests that RFA with or without prior ER is feasible and effective for high-grade dysplasia and mucosal cancer of the squamous esophagus.

To make RFA treatment easier and faster, we evaluated simplified ablation regimens for focal as well as circumferential RFA. The currently used regimens are impractical and time-consuming, as they consist of two ablation passes with extensive cleaning of the ablated zone and the electrode after the first ablation pass, which requires multiple introductions.

In Chapter 8, we have treated 57 patients with three different circumferential balloon-based ablation regimens using the HALO360-electrode (c-RFA) in a multicenter randomized trial. We introduced two simplified regimens, in which we abandoned cleaning of the ablated area and the ablation device, or cleaning of the ablation device alone, after the first ablation pass. The median Barrett’s surface regression at 3 months after c-RFA was comparable using all three regimens, whereas the simplified regimens were significantly faster and required fewer introductions. Thus, c-RFA could be made easier and faster without sacrificing safety or efficacy, by omitting or simplifying the cleaning phase in between ablations.

In Chapter 9, we evaluated a simplified regimen for focal RFA (3x15J/cm² without a cleaning step) using the HALO90-electrode in a multicenter randomized trial. In 40 patients, after randomization of BE areas within 1 patient, one BE area was treated with the simplified regimen and another BE area with the standard regimen for focal RFA. The study showed that the proposed simplified regimen for focal RFA is not inferior to the standard ablation (2x2x15J/cm² with a cleaning step) for the removal of BE islands, and requires fewer introductions, no cleaning step and a shorter procedure time. Therefore, the simplified regimen for focal RFA is recommended for the treatment of residual Barrett’s islands.
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To gain insight into the profile of the small subset of patients who have a poor response to RFA, we assessed the characteristics of 278 patients treated with RFA in a European multicenter cohort study (Chapter 10). ‘Poor initial response’ was defined as less than 50% Barrett’s regression at 3 months after initial c-RFA, graded by two expert endoscopists using endoscopic images. Patients with a poor initial response to c-RFA (13%) had a significantly lower ultimate success rate for eradication of neoplasia and IM, required more treatment sessions during a longer treatment period. We detected four independent predictors of poor initial response: ongoing reflux esophagitis, ER-scar regeneration with BE, esophageal narrowing pre-RFA, and neoplasia in BE for a longer time pre-RFA. These findings need to be confirmed in other study populations. More research should focus on predictors of poor response, to enable the early identification of patients that may benefit from alternative treatment strategies.

Part Three: Single Session RFA and ER

Some patients require a widespread resection to remove all visible lesions prior to RFA. After a more extensive ER, lacerations at the level of the ER scar have been observed during c-RFA in patients. In addition, esophageal narrowing after extensive ER may result in non-uniform electrode contact during RFA. We hypothesized that c-RFA and ER in the same endoscopic session could avoid the impact of scarring on c-RFA and reduce the risk of laceration.

The feasibility of the single-session ER-RFA and RFA-ER approach was studied in a porcine model, as described in Chapter 11. In RFA-ER, the histological assessment of the ER specimen may be hampered by the ablated surface. On the other hand, in ER-RFA, the ablation of the ER wound may carry a higher perforation risk. In a first experiment in 6 pigs, dosage escalation demonstrated that 2x10J/cm\(^2\) was the optimal energy setting during ER-RFA. In a second experiment in 8 pigs, 4 treatment areas in each pig were randomized to: ER-RFA, RFA alone, ER alone, and RFA-ER. In total, two delayed perforations occurred in experiment 1 and 2 after ER-RFA. Remarkably, in the 7 remaining pigs of experiment 2, all 7 ER-RFA and RFA-ER areas showed a severe stenosis versus 5 of 7 areas treated with RFA alone, and none of the areas with ER alone. We concluded that single-session ER-RFA variant was not safe in a porcine model, therefore it seems not ethical to evaluate this approach in humans. Given the high rate of stenosis after RFA-ER and even after RFA alone, we question the validity of the pig esophagus as a model for these experiments.

In Chapter 12, we described a feasibility study of 24 consecutive patients who were treated with single session RFA-ER for lesions in Barrett’s esophagus containing early neoplasia. The median Barrett’s surface regression at 3 months was 95%, and none of the patients required a second c-RFA procedure. Although complete response for neoplasia and IM was achieved in 100% and 95% respectively, 40% of patients required repeat ER for visible lesions during the treatment period. We concluded that c-RFA followed by ER in the same session is feasible, but technically demanding and associated with a substantial rate of complications and repeated ER. This approach, therefore, should be reserved for
highly selected patients who risk severe stenosis after ER, and should be performed by experienced endoscopists. ER followed by RFA after 6 to 8 weeks should remain the standard approach for combined ER and RFA, with esophageal dilations prior to RFA in case of stenosis after widespread ER.