Advances in endoscopic resection and radiofrequency ablation of early esophageal neoplasia
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General discussion and future prospects
GENERAL DISCUSSION AND FUTURE PROSPECTS

This thesis focused on developments in the endoscopic management of early neoplasia in Barrett’s esophagus (BE) using endoscopic resection (ER) and radiofrequency ablation (RFA). In the following paragraphs, we will discuss developments, issues requiring further investigation, and future prospects.

ENDOSCOPIC RESECTION

Endoscopic resection (ER) remains the golden standard as the first step in the work-up of patients with early neoplasia in their Barrett’s segment.\(^1\) We recommend the MBM-technique as the first choice technique for ER, based on our randomized trial in which we compared the ER-cap technique with multiband mucosectomy (MBM) in BE patients with early neoplasia (Chapter 3). Although we did not find a significant difference in safety and efficacy, MBM was significantly cheaper and faster than ER-cap, and potentially easier to learn. For patients with large lesions and suspicion for submucosal tumor infiltration who are unfit for surgery, we advise using the large caliber ER-cap which results in deeper resection and therefore a higher change for radical resection at the vertical margin.

Previously, only patients with mucosal cancer were eligible for subsequent endoscopic management. Nowadays it is becoming more accepted that also for selected BE patients with low risk submucosal adenocarcinoma (T1sm1≤500µm, G1-G2, no lymphovascular invasion) endoscopic treatment is safe and effective.\(^2,3\)

Currently, ER is mainly performed in expert centers, but this may change in the near future. An increase in the incidence of early neoplastic esophageal lesions is expected, given the rising incidence of esophageal cancer, the implementation of endoscopic screening and surveillance programs for Barrett’s esophagus patients, and improved endoscopic imaging techniques. In addition, easier ER techniques such as MBM may make ER more attractive for a wider range of endoscopists.

TRAINING AND CENTRALIZATION OF ENDOSCOPIC RESECTION

In this thesis we have reported our experience with a national ER training program of six teams consisting of an endoscopist, endoscopy nurse and pathologist, aiming at controlled implementation and centralization of ER for early esophageal neoplasia in our country (Chapter 1 and 2). The high rate of complications that occurred, even within the setting of this intensive training program, reflects the complexity of the ER technique. This study underlines why we advocate centralizing of ER treatment in multidisciplinary expert centers: “your surgeon has to know the oncologic nature of the perforation you may cause; your pathologist has to understand the orientation of the ER specimens and the consequences of his histological diagnosis”.

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The ideal profile of an expert center for the treatment of early Barrett’s neoplasia is characterized by an endoscopist with special interest in interventional endoscopy aiming to obtain a tertiary referral function for endoscopic treatment of upper gastrointestinal (GI) neoplasia in a large regional or academic center with an established multidisciplinary expertise in upper GI oncology, demonstrated by a high volume of upper GI-surgery, oncological care, and histopathological expertise.

In addition, centralization of ER cases is required to ensure enough exposure to patients with early Barrett’s neoplasia for all disciplines, since early neoplasia is not frequently encountered in general practice. In this light, we recommend that such centers, a single endoscopist performs the screening, imaging and treatment of all (referred) patients with early upper GI neoplasia, and that a single pathologist evaluates all ER specimens and pre-treatment biopsies. Again, recognizing early neoplastic lesions or irregularities in the BE, with adequate histological assessment of the corresponding biopsy or ER specimen is an extremely important factor in effective endoscopic treatment of early Barrett’s neoplasia. Finally, we advise that national guidelines on the management of early GI neoplasia incorporate requirements of centers offering endoscopic treatment, such as multidisciplinary patient management by a well-trained team, a minimal number of cases per year and prospective case registration.

**TRAINING AND CENTRALIZATION OF RADIOFREQUENCY ABLATION**

Analogous to ER treatment, we strongly advise that RFA treatment is centralized in expert centers. Although RFA is relatively easy to apply, safe and effective RFA treatment depends on appropriate patient selection, high quality endoscopic work-up and imaging, and adequate histological assessment of biopsies and ER specimens. RFA centers should therefore also be proficient in ER, since ER and RFA form a complementary set of treatment techniques for the treatment of early neoplasia in Barrett’s esophagus. Endoscopists that perform RFA should be able to perform ER of a visible or elevated lesion for staging purposes and to render the esophagus flat and suitable for RFA. This holds for patients with early neoplasia as well as for patients with non-dysplastic BE. Further, next to the initial removal of lesions, ER has a role during the RFA treatment period, for the removal of persisting BE areas after RFA treatment, or to remove suspiciously looking lesions that ‘pop-up’ during the RFA treatment period. In Europe, we have successfully implemented ER and RFA training programs (www.endosurgery.eu, www.rfa-academia.eu), which have set the standard for uniformity in training endoscopic management of early upper GI neoplasia.
General discussion and future prospects

ENDOSCOPIC TREATMENT OF WIDESPREAD LESIONS

For patients with widespread neoplastic lesions in BE the optimal management strategy remains unknown. Although the combined approach of ER followed by RFA after 2 months is safe and effective in case the ER size is limited to 2 cm and less than 50% of the circumference (Chapter 4 and 5), studies thus far have excluded patients with widespread lesions. After extensive ER, scarring and stenosis occurs, which may result in non-uniform electrode contact or superficial laceration during RFA. However, there is a subset of patients that simply require a widespread ER to completely remove the non-flat component and to guarantee optimal staging. For these patients, four endoscopic treatment approaches are available: 1) the standard approach of ER followed by RFA after 2 months, with RFA preceded by dilation sessions in case of ER-induced stenosis, 2) single session RFA and ER, 3) stepwise radical endoscopic resection (SRER), 4) endoscopic submucosal dissection (ESD). Importantly, it should be realized that in patients with widespread lesions, the incidence of submucosal cancer or unfavorable tumor characteristics detected in ER specimens requiring esophagectomy may be higher.

Single session RFA and ER is a feasible approach for patients with widespread lesions (Chapter 12), however the rate of repeat ER after treatment was relatively high and the rate of complications was substantial. It is possible that this study population comprised more complex cases and patients with more comorbidity as compared to other studies with more strict inclusion criteria. Nevertheless, we advise that the single session RFA and ER approach should be reserved for selected individual cases with widespread lesions and should be performed in expert centers only.

SRER and ESD are both complex techniques that require training and experience and are associated with higher rates of stenosis, bleeding and perforation compared to ER and RFA. Although SRER is associated with a much higher stenosis rate compared to combination therapy with ER and RFA (88 versus 15%) (Chapter 5), SRER may be suitable for patients with more extensive lesions in BE ≤5 cm. The ESD technique has the theoretical advantage over SRER that it allows for en bloc resection of large lesions, which favors adequate histological assessment of the specimen. However, the experience with esophageal ESD in the western is still limited and results are generally disappointing with R0-resection rates below 50%. In addition, ESD is not suitable for complete BE removal, given the high stenosis rate of ESD and the tortuous anatomy of the gastroesophageal junction, often with a fibrotic submucosa due to reflux damage. Therefore, we do not expect a major role for ESD in the treatment of early BE neoplasia in the near future. On the other hand it is undeniable that ESD for early GI neoplasia is gaining interest. We expect that more western endoscopists will start performing ESD despite a low caseload. Ongoing discussions concern questions such as how to provide adequate training and how to set quality standards in ESD.

Presently, we advise that for patients with widespread neoplastic lesions in BE, eligible for endoscopic treatment, the standard approach of ER followed by RFA after 6-8 weeks is used. In case a symptomatic or circumferential stenosis develops preventing subsequent RFA, stepwise dilation is performed up to 18-mm to allow for subsequent circumferential...
RFA of the remaining BE. For patients with widespread neoplastic lesions in short segment BE, a single session approach of extensive ER immediately followed by focal RFA of any residual BE tongues or islands with the HALO\textsuperscript{90}-device, avoiding ablation of the ER-wound, may be a suitable alternative.

The endoscopic treatment of early esophageal lesions would really make a step forward if we find ways to prevent stenosis and scarring after ER, SRER and ESD. Highly interesting are the recent studies from Japan that show a much lower stenosis rate after repeated sessions of corticosteroid injections in the resection wound, or oral administration of corticosteroids for several weeks after ESD.\textsuperscript{9,10} The use of such preventive measures to prevent stenosis is currently under investigation in our center using animal models.

**RADIOFREQUENCY ABLATION**

In the past five years several clinical trials have established the excellent safety and efficacy rates of RFA, resulting in complete eradication of all intestinal metaplasia (IM) and early neoplasia in 77-100\% of patients.\textsuperscript{11-15} Large-scale RFA registries have confirmed the safety and efficacy of RFA.\textsuperscript{16,17} The cost-effectiveness of RFA for BE containing high-grade dysplasia (HGD) has been established using a cost-utility model.\textsuperscript{18,19} In the meantime, RFA has been implemented as an accepted endoscopic treatment modality in more than 1,000 centers worldwide. The number of patients treated with RFA has increased spectacularly, counting over 44,000 patients by now.

Other ablation modalities for early neoplastic BE are photodynamic therapy (PDT), argon plasma coagulation (APC) and cryoablation. PDT has been largely abandoned in the past years because of the high rate of stenosis and buried glands, photosensitization, and poor efficacy compared to RFA.\textsuperscript{20,21} APC for complete BE removal resulted in a high rate of recurrent IM and stenosis.\textsuperscript{22} APC is currently only used as an adjuvant therapy, to remove residual tissue bridges during piecemeal ER, or to ablate small residual islands of BE <5mm after RFA, since APC is faster and cheaper than a new focal RFA session. Spray cryotherapy has shown to be effective for BE patients with early neoplasia, however eradication rates of dysplasia and recurrence rates seem inferior to RFA.\textsuperscript{23,24} Recently, a new balloon-based device for cryoablation has been introduced, consisting of a compliant balloon, which may be of benefit in patients with post-ER or reflux stenosis. Currently, safety studies are performed in human patients using a pre-esophagectomy model.

**SIMPLIFYING RADIOFREQUENCY ABLATION**

The currently used RFA ablation regimens are rather impractical, consisting of several small steps and multiple introductions of the endoscope and ablation devices. We therefore have developed simplified ablation protocols, eliminating the time-consuming cleaning step of the ablated area and electrode.

For circumferential balloon-based RFA, we now recommend the use of the *simple-no-clean* regimen (2x12J/cm\textsuperscript{2} without cleaning) for patients with an uncomplicated straight
esophagus (Chapter 8). For patients with a ‘complicated’ esophagus, e.g. a tortuous course or extensive scarring or stenosis, we advise to adhere to the standard ablation regimen. In these patients, the cleaning step allows for inspection of the ablation effect and the detection of skipped zones, which can be targeted during the second ablation pass. For focal RFA using the HALO\textsuperscript{90}-device, we recommend the use of the simplified regimen (3x15J/cm\textsuperscript{2} without cleaning) for residual BE islands (Chapter 9). Both simplified ablation regimens make RFA easier and faster with fewer introductions of devices and may thus diminish patient discomfort.

In future studies of focal RFA regimens, patients instead of BE areas should be randomized to allow comparison of safety and procedure time. We still lack data on the outcome of focal ablation with 3x15J/cm\textsuperscript{2} in which all residual BE and the neo-squamocolumnar junction is treated with this regimen at multiple endoscopic treatment sessions. Possibly, a simplified ‘triple’ regimen for focal RFA at 12 J/cm\textsuperscript{2} instead of 15 J/cm\textsuperscript{2} may be a safer and equally effective alternative. In the US, the current energy setting for focal RFA is 12 J/cm\textsuperscript{2} while using the standard regimen (2x12J/cm\textsuperscript{2} - cleaning step - 2x12J/cm\textsuperscript{2}). A triple application at 12 J/cm\textsuperscript{2} is also used for focal RFA in patients with early squamous neoplasia, based our study experiences in China, in which stenoses were encountered using higher energy settings or more applications. Focal ablation using the longer HALO\textsuperscript{90-ULTRA}-electrode was not found to be very effective at 2x12J/cm\textsuperscript{2} with a cleaning step, therefore also for HALO\textsuperscript{90-ULTRA}-ablation, a step-up to 3x12J/cm\textsuperscript{2} is currently considered. A triple 12 J/cm\textsuperscript{2} regimen for all the abovementioned indications and devices does not appear illogical. New studies are currently designed to address these hypotheses aiming at further simplification and optimization of focal RFA.

**OTHER ADJUSTMENTS OF THE RFA TREATMENT PROTOCOL**

Future improvements of RFA may come from new types of the HALO\textsuperscript{90}-electrode, such as the smaller HALO\textsuperscript{60}-electrode that is easier to introduce, and the HALO\textsuperscript{90-ULTRA}-electrode that facilitates ablation of the neo-z-line (neo-squamocolumnar junction). This may be an important improvement given the reported findings of focal IM at the neo-z-line after RFA treatment.\textsuperscript{25-27} At this time, we standardly perform circumferential ablation of the neo-z-line with the HALO\textsuperscript{90}-electrode at least once during the RFA treatment period, since we feel that this approach is valuable for the eradication or prevention of IM after RFA at this area. The neo-z-line, located at the level of the gastric cardia, is sometimes located in a tortuous distal esophagus, where a short HALO\textsuperscript{90}-catheter is more difficult to position across the neo-z-line than the longer HALO\textsuperscript{90-ULTRA}.

Further, a more compliant HALO\textsuperscript{360}-balloon would make circumferential balloon-based RFA easier if the sizing step could be abandoned and more effective in case the balloon would fit to small irregularities or caliber changes of the esophageal wall. The practicality of the procedure would also benefit from the development of ablation devices that can be introduced through the working channel of the endoscope instead of being introduced alongside the endoscope or attached to its distal tip.
RFA FOR BARRETT’S ESOPHAGUS CONTAINING LOW-GRADE DYSPLASIA

RFA treatment for BE containing low-grade dysplasia (LGD) is controversial because the risk of malignant progression in LGD is not established. The reported progression rates in LGD vary from 0.6% in unselected LGD cases to 28% for patients in whom two or more pathologists have agreed on the LGD diagnosis.\textsuperscript{28-31} These varying results likely reflect differences in the number of pathologists that had to agree on the diagnosis, the high interobserver variability associated with LGD, and differences in study populations. In our center we have followed a cohort of patients in whom the LGD diagnosis was confirmed by two expert endoscopists under surveillance according to recent national guidelines. In this cohort, the incidence rate of HGD or carcinoma was as high as 13.4% per patient per year.\textsuperscript{28} In a subset of patients with such a high progression rate to HGD or carcinoma, RFA treatment may be justified and cost-effective.\textsuperscript{19} Currently, the SURF-trial is underway, in which patients with a confirmed diagnosis of LGD are randomized to surveillance versus RFA treatment. This multicenter randomized trial will give essential information on the malignant progression rate of LGD and the efficacy of RFA in preventing this, as well as the impact of the two approaches on quality of life.

RFA FOR NON-DYSPLASTIC BARRETT’S ESOPHAGUS: IS IT JUSTIFIED?

Based on new data on the durability of BE eradication with RFA and a lower progression rate of non-dysplastic BE (NDBE) to carcinoma, a recent cost-effectiveness analysis concluded that RFA is not a cost-effective approach for NDBE.\textsuperscript{19} Nevertheless, RFA is offered to patients with NDBE in several centers. In our opinion, RFA should not be standard treatment for NDBE patients, but selected NDBE patients may benefit from RFA, such as young patients with a long life expectancy, a long segment BE, and a positive family history of esophageal adenocarcinoma. The impact of RFA on quality of life may also be important, if future studies confirm that RFA for NDBE reduces the patient’s fear of cancer.\textsuperscript{32}

Several research groups currently focus on potential genetic and histological markers as well as patient characteristics relating to malignant progression of BE, to enable risk stratification of NDBE patients.\textsuperscript{33} Further, the quality of surveillance programs and/or the use of chemoprevention, in addition to PPI treatment may significantly modify the balance between endoscopic surveillance or prophylactic ablation.\textsuperscript{34} Large prospective surveillance cohorts such as the Barrett’s surveillance cohort in general hospitals in the Amsterdam region will be of great importance to answer the question if RFA of NDBE is justified. Currently our research group works on a retrospective study looking at the baseline biopsy characteristics of patients that progressed from NDBE to HGD of...
carcinoma. Until better risk stratification of NDBE patients is available, RFA for NDBE should not be considered standard of care.

**DURABILITY OF RFA**

Long-term follow-up is the most important missing information relating to RFA treatment. The most favorable situation would be a permanent eradication of IM and early neoplasia. This would justify prolonged surveillance intervals, less rigorous biopsy protocols, or even abandoning endoscopic surveillance at all. The durability of the treatment effect is an important factor in cost-effectiveness, and thus affects the range of indications for RFA treatment. Currently, all three follow-up studies have reported high rates of sustained remission. After 3-5 years of follow-up, sustained complete removal of neoplasia and IM was shown in 94-98% and 91-100% of patients, respectively.\textsuperscript{25,26,35}

The favorable long-term results of these studies demonstrate that the result of RFA treatment, with or without prior ER for visible lesions containing early neoplasia, is durable in the vast majority of patients. It, however, also shows that long-term endoscopic follow-up is required for these patients. For patients with a low baseline risk (e.g. NDBE) however, these long-term results may suggest that prolonged surveillance is not required after RFA.

**INTESTINAL METAPLASIA IN THE CARDIA**

Another question is the clinical relevance of focal IM in gastric cardia after RFA treatment. During 5-years follow-up after RFA for early BE neoplasia in patients treated at our center, focal IM was found in gastric cardia biopsies in 35% of patients, obtained during any follow-up endoscopy.\textsuperscript{25,26,35} We obtain 4-quadrant biopsies immediately distal to the neo-squamocolumnar junction in all patients, to assess if all Barrett’s mucosa has been removed. Endoscopic differentiation between gastric mucosa and IM is hardly possible, and this area has an increased risk of recurrences. To prevent residual IM at the squamocolumnar junction, we perform circumferential HALO\textsuperscript{90}-ablation of the neo-squamocolumnar at least once during the RFA treatment period. Findings of IM in the cardia after successful endoscopic treatment of early Barrett’s neoplasia may reflect insufficient treatment, recurrent disease, or it may be an irrelevant physiological finding. Since the incidence of IM in the cardia does not increase over time, and is mostly observed in a single biopsy in a single patient, we hypothesize that IM of the cardia does not result from ongoing reflux after treatment, and therefore does not reflect residual disease.\textsuperscript{35} Furthermore, IM of the cardia can be detected in biopsies of 25% of the normal population and is generally not considered a premalignant condition.\textsuperscript{36} Although the clinical relevance of focal IM of the cardia after RFA remains unknown, our long-term data do not suggest that it relates to residual or recurrent BE.
General discussion and future prospects

BURIED BARRETT’S GLANDS

Some fear that buried Barrett’s glands underneath neosquamous epithelium after prior RFA may progress to an advanced malignant stage while remaining endoscopically invisible. The incidence of buried glands after RFA in normal appearing neosquamous epithelium is however very low, especially when compared to patients after PDT and APC. In addition, findings of buried glands may reflect a false-positive histological diagnosis in tangential sectioned biopsies of accidentally sampled residual Barrett’s islands, or biopsies obtained at the neo-z-line where there is a small overlap of 4-8 mm between squamous and gastric type mucosa. With the ongoing discussion on buried glands, also the adequacy of biopsying remains topic of debate. A study from our center showed that the biopsy depth of treated and untreated squamous epithelium is similar, with presence of the lamina propria in one-third of biopsies independent of epithelial type. In those rare cases in which buried glands are diagnosed, we recommend detailed inspection of the neosquamous mucosa with narrow band imaging. In case residual BE is detected, focal treatment of this area is indicated. In case there is no visible BE, biopsies should be repeated. When presence of buried glands is histologically confirmed once again, focal RFA may be used to eradicate the buried glands. We have encountered this situation only once over the last seven years. Given the favorably high rates of sustained complete removal of neoplasia and IM after 3-5 years follow-up and the low rate of 0.1% buried glands in our RFA cohorts, we assume that the clinical relevance of buried glands is limited.

RECOMMENDATIONS ON FOLLOW-UP

Since the durability of the RFA is not a 100%, continuous surveillance of patients after RFA is required in patients treated for HGD or early cancer. Most centers adhere to half-yearly surveillance interval after early neoplasia at baseline. In addition, after the first year we adhere to a yearly surveillance interval.

In our opinion, it is justified to abandon random biopsies from the neosquamous epithelium, provided that meticulous inspection of the neosquamous epithelium with high resolution endoscopy and narrow band imaging is performed by an endoscopist with a trained eye. Targeted biopsies should still be obtained from any visible abnormalities in the neosquamous epithelium. Meticulous inspection of the neo-squamocolumnar junction (neo-z-line) is also required given the high rate of recurrence at this area. For this reason, and since endoscopic differentiation between gastric mucosa and IM is not reliable, biopsies immediately below the neo-z-line (<5mm) should be obtained. To establish the guidelines on surveillance intervals after RFA, more data are required on the long-term follow-up durability of response to RFA and on factors that affect the durability.
POOR RESPONDERS TO RFA TREATMENT

Although RFA is a highly effective treatment modality, occasionally patients demonstrate a poor response to RFA. These patients generally present with little regression of their BE segment despite RFA, or show persistent inflammation at three months after RFA. We found that patients who had less than 50% BE surface regression at three months after initial circumferential RFA, ultimately had a lower success rate for complete response for IM and early neoplasia, required more RFA sessions, and a longer treatment period (Chapter 10). This poor initial response to circumferential RFA was predicted by the following factors: regeneration of the ER wound with BE, presence of neoplasia in BE for a longer time period prior to RFA, and a relative narrowing of the esophagus prior to RFA. Recently, a relationship was suggested between uncontrolled reflux despite PPI treatment and failure for CR-IM.39

Patients who demonstrate a poor response to RFA may benefit from an alternate treatment approach in the future, depending on the cause of poor response. Potential approaches are fundoplication followed by RFA and stepwise radical endoscopic resection (SRER). Further research is necessary to elucidate the mechanisms underlying the lack of response to RFA in this small subgroup, and to better predict which patients will be these poor responders to RFA treatment.

RFA FOR EARLY SQUAMOUS NEOPLASIA OF THE ESOPHAGUS

The combined treatment of ER and RFA can also be used for treatment of squamous neoplasia of the esophagus. We have reported a prospective case series of 13 patients with early squamous neoplasia that were successfully treated with ER and RFA in our center (Chapter 7). Subsequently, prospective trials were started in China, in a region where esophageal squamous cell cancer has a very high incidence. A first trial in 29 patients with flat-type HGD or early squamous cell cancer treated with RFA treatment resulted in eradication of neoplasia in 97% of patients, and an acceptable safety profile with 4 strictures resolving upon dilation.40 In regions with a high incidence of squamous cell carcinoma, and limited endoscopic expertise, an easy-in-use technique with such a high efficacy rate and an acceptable safety profile may have a significant impact. Future research should focus on finding optimal energy settings and regimen for the squamous esophagus, how to combine ER and RFA, and the impact of Lugol’s staining on the outcome of RFA. The most recent data suggest that for circumferential ablation a single 12J/cm² application suffices, whereas a 3x15J/cm² regimen is preferred for focal ablation, and cleaning of the ablation zone is not required. Using these regimens, RFA should always be preceded by Lugol’s staining in the same session.
SUMMARY

ER remains the first step in the endoscopic management of early Barrett’s neoplasia, with a therapeutic as well as diagnostic purpose. ER followed by RFA is the standard endoscopic approach for patients with early Barrett’s neoplasia. Simplified ablation regimens make RFA easier and faster while maintaining the efficacy of RFA. Endoscopic treatment of early Barrett’s neoplasia should be centralized in expert centers, after adequate training in ER and RFA. Future research should focus on predicting response to RFA treatment, and how to optimize the regeneration process after RFA. An important other focus for research is the risk stratification of patients with LGD and NDBE to enable selective use of RFA as a prophylactic treatment.
REFERENCES


