Endoscopic eradication of Barrett's oesophagus with early neoplasia
Pouw, R.E.

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FUTURE PROSPECTS
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As described in this thesis, endoscopic treatment has steadily gained its place as the therapy of choice for patients with early Barrett’s neoplasia. From endoscopic resection (ER) monotherapy, which was abandoned due to a high recurrence rate of neoplasia in residual Barrett’s mucosa, we moved into the field of complete Barrett’s eradication to prevent recurrences. After disappointing results of photodynamic therapy for this purpose, we used stepwise radical endoscopic resection (SRER) to remove the entire Barrett’s segment during subsequent resection sessions. Although SRER proved highly effective, a European multicentre study showed that SRER is technically demanding and associated with a high rate of oesophageal strictureting especially in patients with longer Barrett’s segments. We therefore evaluated the use of a relatively new endoscopic ablation technique, radiofrequency ablation (RFA). The initial promising results of RFA to eradicate all Barrett’s mucosa with early neoplasia were reproduced in a number of large-scale European multicentre studies. Given its high efficacy, safety and relatively easy application, RFA with or without prior ER for visible lesions, has been implemented as the treatment of choice in a number of national and international guidelines. The studies described in this thesis have made an indispensable contribution to the evidence on which current management of early Barrett’s neoplasia is based. However, we should always strive for improvement. In the following paragraphs we will therefore make recommendations to improve Barrett’s management in the future, and we will speculate on studies that may help to reach these improvements.

1. Indications for endoscopic treatment in patients with Barrett’s oesophagus

High-grade intraepithelial neoplasia (HGIN) and mucosal cancer

Based on the currently available literature from different centers around the world, and the studies presented in this thesis, there is enough evidence that endoscopic treatment, with ER as its cornerstone, is the treatment of choice for BO patients with HGIN and mucosal cancer, with 5-yr disease free survival in up to 95% of patients.

Low-risk submucosal cancer

Barrett’s cancer infiltrating the submucosa is still regarded as an indication for surgery, given the risk of lymph node metastasis (N+) ranging from 0-22% for sm1, and 36-54% for sm2/3 cancer. These risk estimates are, however, based on retrospective cohorts with submucosal cancer diagnosed in surgical resection specimens. At the time these studies were performed, oesophagectomy was the treatment of choice for any grade of neoplasia, ranging from a single biopsy diagnosis of HGIN, to stage T3 cancer. Accurate histological differentiation between different depths of submucosal invasion did therefore not bear much clinical relevance. Surgical specimens were routinely cut in 5-10 mm slices and the area of deepest infiltration could have been missed easily. This may have resulted in underestimation of invasion depth, and thus a wrong interpretation of the N+ risk corresponding with a certain depth of invasion. In contrast, when infiltration depth is assessed in ER-specimens, which are routinely cut in 2-mm slices with additional cuts in case of submucosal invasion, the N+ risk for certain infiltration depths can be reported more accurately. This has already been demonstrated by the fact that the 4-12% risk of N+ for mucosal cancer reported in surgical
series, is in fact much lower (<0.5%) when the diagnosis is based on ER-specimens.\textsuperscript{8} As reported by Manner et al.,\textsuperscript{14} and Alvarez Herrero et al.,\textsuperscript{15} the risk of N+ in ‘low-risk’ submucosal cancer diagnosed in ER-specimens, may also be lower than reported thus far. Low-risk criteria are defined as well to moderately differentiated cancer, with submucosal invasion of ≤500 µm, without signs of lymph-vascular invasion. Taking into account that the N+ risk may be lower than reported thus far, and that most patients with low-risk submucosal cancer are elderly with co-morbidities, endoscopic treatment should be considered as a valid alternative to surgery in these cases. Until more evidence is available, we think that an approach of endoscopic treatment with 3-monthly follow-up with endoscopy and EUS is an acceptable in patients with low-risk submucosal cancer, who are not optimal candidates for surgery. Studies comparing endoscopic treatment for low-risk submucosal cancer to surgery in a randomized setting will be difficult, since patients are rare, often have contraindications for surgery and may not always agree to participate in such a study. A study with ER for staging of the disease, followed by surgery to assess for lymph node metastasis also has its drawbacks, since micro-metastases and lymph node metastases can be missed. Therefore, multicentre prospective registration of endoscopically treated low-risk submucosal cancer, with endoscopic and EUS follow-up, will be important to evaluate if endoscopic treatment is indeed a valid alternative to surgery for selected patients.

**Low-grade intraepithelial neoplasia (LGIN)**

Recent data have demonstrated that after expert histological revision, the diagnosis of LGIN is down-staged in the majority of patients.\textsuperscript{18} If LGIN is confirmed by expert histological revision, however, it is a serious disease with a cumulative risk for developing HGIN or cancer of 83% within 97 months.\textsuperscript{16} Recent AGA-guidelines have indicated that RFA may be a therapeutic option for treatment of confirmed LGIN in BO to prevent neoplastic progression, despite the controversies surrounding the definition of LGIN.\textsuperscript{19} For LGIN in BO, Shaheen et al. and Sharma et al. demonstrated that RFA achieved eradication of all LGIN and intestinal metaplasia (IM) in 90-100% and 81-90% of patients, respectively.\textsuperscript{16,17} Another randomized trial performed in a multicentre European setting, is currently underway comparing RFA versus surveillance for patients with confirmed LGIN (SURF-study). Given these recent developments, an approach using RFA to eradicate BO in patients with confirmed LGIN, will most likely be adapted in the near future. In that case, there will be an increased need for expert histological revision of LGIN, or preferably for more objective markers of LGIN, such as biomarkers.

**Non-dysplastic Barrett’s oesophagus (NDBO)**

Currently an approach of endoscopic surveillance with biopsies is used to detect malignant progression in these patients. However, surveillance is limited by the difficulty to detect early neoplasia endoscopically, by biopsy sampling error, by inter-observer variability between pathologists, and by questionable cost-effectiveness.\textsuperscript{20} The annual progression rates to HGIN (0.9%) or cancer (0.5%) are relatively low.\textsuperscript{21,22} Biomarkers predicting malignant progression may therefore help to identify those patients with an increased risk to develop neoplasia. These patients could then undergo more frequent endoscopic surveillance or prophylactic ablation of their NDBO. Currently, ablation of NDBO is still a subject of much debate given the low progression rates and lack of objective predictors for progression. However, if the annual progression risks are accumulative, as suggested by a recent Dutch nation-wide cohort study,\textsuperscript{23} then patients with a longer life expectancy will have a serious risk to develop cancer at some point in their life. This knowledge, as well as the promising preliminary results in the field of prognostic biomarkers\textsuperscript{24-28} and the demonstrated efficacy and safety of RFA, may be used to improve current management of NDBO. Clearly, endoscopic surveillance with its previously mentioned shortcomings is not efficient enough to halt the rising incidence of oesophageal adenocarcinoma.\textsuperscript{29} Therefore, alternatives such as prophylactic ablation of NDBO using RFA deserve to be evaluated.

The use of RFA to prevent neoplastic progression in NDBO compared to standard endoscopic surveillance should ideally be studied in a randomized setting. Given the relatively low annual progression rate, a large cohort of patients would be needed, warranting a multicentre setting. Preferably, only patients recently diagnosed with NDBO should be included in such a study, since these are the patients that best reflect day-to-day practice. These patients have the highest chance of under-diagnosis due to sampling error, and thus a higher risk of progression compared to patients who have already undergone multiple surveillance endoscopies. Furthermore, anticipating on the implications of such a study, its results will be used to make a decision between RFA versus surveillance in these recently diagnosed patients.

The primary outcome parameter for such a randomized study should be progression to HGIN or early cancer, both currently indications for treatment. However, with the recent developments in the field of RFA for LGIN, one may question if patients diagnosed with LGIN at some point, are still willing to remain under endoscopic surveillance instead of undergoing RFA.

In the future, the decision to use prophylactic RFA in patients with NDBO will likely be guided by the use of biomarkers to identify those patients with an increased risk of malignant progression. For now, we think that RFA for NDBO may be considered for individual patients who are expected to have an increased risk for neoplastic progression, for example patients with a long BO segment, patients with a strong family history of oesophageal adenocarcinoma, and young patients with a significant life-expectancy. Quality of life may also play an important role in the decision to treat patients diagnosed with NDBO, since fear of developing cancer may negatively influence quality of life, especially in patients with a family history of Barrett’s cancer.\textsuperscript{20} Although surveillance after RFA will still be necessary since no long-term follow-up data after RFA for NDBO are available yet, the risk of malignant progression and patients’ fear to develop cancer, may be significantly decreased.

2. **Endoscopic work-up of patients with early neoplasia in Barrett’s oesophagus**

Work-up prior to endoscopic treatment usually consists of thorough endoscopic inspection, often using advanced imaging techniques, to detect mucosal irregularities. Targeted biopsies are then obtained from any abnormalities, as well as randomly throughout the BO. Often, a second endoscopy is scheduled to remove abnormalities by ER, followed by one or two additional endoscopies to re-stage the residual BO with biopsies prior to RFA. Chapter 4 showed that in all patients undergoing SRER, the histological findings of the first procedure corresponded with the overall worst histopathology of the patient: all T1sm1 cancers were identified as a suspicious lesion and removed during the first procedure and
no G3/G4 cancers or lymph-vascular invasion were diagnosed at subsequent ER sessions. This suggests that after thorough endoscopic work-up and ER of the most involved area with histological correlation, the remaining BO can be safely ablated without significant risk of leaving submucosal lesions undiagnosed and under-treated. The chance of finding early cancer in random biopsies from normal appearing flat-type mucosa is extremely low. Although not officially reported, no patients were excluded from any of the studies in this thesis based on this exclusion criterion.

In the future, endoscopic work-up may be performed more efficiently. Thorough endoscopic inspection can be performed to detect any mucosal irregularities that may be immediately removed by ER for histological staging. If the ER specimen does not show risk factors for lymph node metastasis, endoscopy can be performed after 6 weeks to inspect the ER-wound and to evaluate if there are any other mucosal abnormalities. If no other lesions are observed, the residual Barrett’s mucosa can be treated with RFA, without the need to obtain additional random biopsies. Also, in between RFA sessions, there will be no need to obtain biopsies from normal appearing flat-type mucosa. During work-up for endoscopic treatment, high-definition endoscopy allowing for wide-angle inspection of the oesophagus may therefore be more useful than advanced imaging techniques allowing for detailed, focal inspection of the mucosa (e.g. confocal endomicroscopy and spectroscopy).

3. Developments in endoscopic resection

As demonstrated in chapter 3, multiband mucosectomy (MBM) was equally effective and safe as ER-cap for piecemeal resection of early BO neoplasia, however, significantly faster and cheaper. In the future, the use of the ER-cap technique will in our opinion only be indicated for patients with large lesions or lesions suspicious for submucosal invasion who are unfit for surgery and in whom the first ER will be their best shot for curative resection. In those cases, the large flexible cap should be used to increase the chances of radical resection, in case the lesion actually extends into the submucosa.

MBM did result in significantly smaller resection specimens than ER-cap, which may imply that more adjacent resections should be performed to remove a lesion. Piecemeal ER does not allow for histological assessment of radicality at the lateral resection margins. However, as long as the visible lesion is completely removed and histological evaluation shows radically removed neoplasia at the deep resection margins, the lateral margins may be less relevant, since residual Barrett’s mucosa will be treated additionally by RFA. Endoscopic submucosal dissection (ESD), does allow for en-bloc resection of neoplastic lesions. However, the advantage of using ESD compared to ER in BO may be limited. First, ESD may be effective and safe for radical removal of neoplastic lesions in the stomach or squamous oesophagus, but radical resection rates for Barrett’s neoplasia from Western series (22-64%) are quite disappointing. ESD in BO is technically much more challenging than ESD in the stomach or squamous oesophagus, due to submucosal fibrosis resulting from reflux oesophagitis, and ESD at the GO-junction is extremely difficult due to the angulated anatomy at this level. Second, in contrast to piecemeal ER, ESD allows for en-bloc resection. However, as described above, if neoplasia is removed radically in the deep resection margins, histological evaluation of the lateral margins may be less relevant since the residual BO mucosa needs to be treated anyway. ESD will not be applicable for complete BO removal, given the high stricture rates associated with widespread ESD. Third, although ESD results in less local recurrences, the local recurrence rates after ER followed by RFA are so low that the potential benefit from applying ESD may be limited. Fourth, just as after ER, follow-up is still indicated after ESD to detect recurrences in the oesophagus and cardia at a curable stage. All in all, ESD in its current form will have a limited role in the management of early BO neoplasia.

4. Developments in endoscopic ablation

Although RFA is relatively easy to apply, and operator dependency is limited by standardization of RF energy delivery, the technique may be improved at some points. First, a flexible ablation balloon should be developed, which fits through the working channel of an endoscope, and which adjusts itself to the oesophageal diameter. This would make the sizing step, placement of a guide-wire, and repeated introductions with the endoscope redundant. Second, the energy settings for ablation may need to be re-evaluated. Currently the HALO90 catheter is used at 2x 12 J/cm², and the HALO90 at 2x2 15 J/cm² in Europe and 2x2 12 J/cm² in the US. In our first studies we demonstrated that thorough cleaning of the ablation zone in between ablations increases efficacy. However, this cleaning step requires additional procedure time and patience from the endoscopist. Although a second ablation pass will remain necessary to treat any areas that were skipped during a first ablation pass, increasing the energy settings might make the cleaning step unnecessary, while maintaining the same depth of ablation. Two randomized studies comparing efficacy of ablation in patients undergoing HALO90 or HALO90 ablation with extensive cleaning in between ablations vs. no cleaning, are currently being performed at our centre. Up to now, RFA is the only technique that has been proven to be safe and highly effective for eradication of BO. Photodynamic therapy should be abandoned for Barrett’s ablation, given its poor efficacy and significant complication risk. APC is an effective, easily accessible and cheap ablation tool, but for ablation of an entire BO segment it is just not very practical. For ablation of small islands, however, APC is faster and cheaper compared to HALO90 ablation. In all patients not treated within an RFA-study protocol, we use APC for residual islands with a maximum diameter of 5 mm, and a maximum of 3 residual islands. Another ablation tool undergoing interesting developments is cryoablation. Initially cryospray-ablation was used for Barrett’s ablation. However, since the liquid nitrogen was sprayed on the mucosa from a certain distance, for a certain amount of time, results were very operator dependent. Recently, a balloon-based device has been developed for cryoablation. This flexible balloon adjusts itself to the oesophageal wall and is then filled with liquid nitrogen, freezing all mucosa in contact with the balloon. However, to surpass the current efficacy and safety profile of RFA, this technique should be able to reach the same constant depth of ablation, it should be well tolerated by patients, easy to use, and affordable. Lastly, we should define when additional HALO90 treatment for residual Barrett’s islands should be ceased. After HALO90 ablation, at least one HALO90 procedure should be performed to circumferentially ablate the entire gastro-oesophageal junction, and any residual BO islands. If large islands persist, a second HALO90 procedure can be performed. However, if there are still residual islands of BO after the second HALO90 procedure, this may indicate that contact between the electrode and mucosa in these areas is suboptimal. Removing such...
residual areas by MBM may be much faster, cheaper and more effective. As demonstrated in chapter 10, MBM can be applied without problems after prior RFA. 28 As mentioned above, small islands <5 mm can also be touched up with APC.

5. Management of patients with widespread neoplastic lesions
Scarring after ER makes subsequent RFA more challenging, due to a more difficult sizing procedure, suboptimal contact between mucosa and electrode, and an increased risk of mucosal laceration and stenosis. As described in chapter 7, we found fewer complications when the extent of ER was limited to 2 cm in length, and 50% of the oesophageal circumference. 1 In most patients, visible lesions can be removed within this restriction; however, in some patients more extensive resection is necessary. The most effective treatment approach to reach eradication of neoplasia and all Barrett’s mucosa will be SRER if the BO is <5 cm in length. 4,36 However, for patients with a BO >5 cm, another solution should be found to combine widespread ER and RFA, while minimizing the risk of suboptimal treatment, mucosal laceration or stenosis. We already evaluated the use of circumferential RFA, followed by ER of irregular mucosa in the same session, in a small series of 24 patients. Although circumferential RFA could be performed uncomplicated in all patients, and histological specimens allowed for assessment of neoplastic invasion depth, this approach required some skill from the endoscopist and pathologist. 37 Preferably, we would like to perform ER of visible lesions first, followed by RFA in the same session, before scarring of the ER-wound occurs. In pig studies, however, this approach was associated with severe strictureing and even perforation (unpublished data). The optimal approach to combine ER and RFA in the same session should therefore be studied better. Until then, a sequential approach of widespread ER followed by dilations until 18 mm to allow for RFA using an 18-mm catheter, may be the best option to treat widespread mucosal irregularities in BO >5 cm.

6. Neosquamous regeneration after RFA
The process of regeneration and factors that contribute to conversion of BO into neosquamous epithelium after RFA are still poorly understood. Some patients undergoing RFA require only a single treatment session for complete reversion of their BO into neosquamous epithelium whereas others show poor healing without significant regression. There are several hypotheses concerning the origin of the neosquamous epithelium after ablation therapy: outgrowth from existing pools of squamous cell progenitors, repopulation from adjacent areas with squamous epithelium, or regeneration from multipotent progenitor cells from the esophageal glands or bone marrow. 28-32 Further insight of this process of squamous repopulation after RFA would be valuable for two reasons. Firstly, it might help to identify patients with an anticipated poor response to RFA and/or to intervene in the regeneration process. Secondly, it may answer the question if eradication of BO by RFA results in permanent clearance of genetic abnormalities of the epithelium and thus in a reduced risk to develop cancer.

Studies to increase our insight into neosquamous regeneration after RFA have been initiated, however, to get to the bottom of this intriguing matter expertise from different centers should be combined.

7. Predictors of response to RFA
Sporadically, we encounter patients with poor response after the first RFA treatment. These patients show minimal or slow regression of the Barrett’s epithelium after RFA, and some of these patients show delayed healing of the ablated areas. As described above, factors responsible for wound healing and response to RFA treatment are still unknown. By prospective registration of a variety of factors for all patients treated with RFA e.g. BO length, grade of dysplasia at baseline, smoking, healing after ER, etc, we hope to be able to identify factors that may predict who will respond well to RFA treatment, and in whom treatment will be difficult and will require more time.

8. Management of reflux after endoscopic treatment of BO
BO is a complication of longstanding gastro-oesophageal reflux. Although no one has ever seen a BO ‘develop’, one may question if PPI treatment after successful eradication or BO is enough to prevent recurrence. Currently, 5-year follow-up data have shown minimal recurrence of Barrett’s mucosa, which suggests that PPI treatment is sufficient. 33-35 However, in patients with therapy resistant reflux, or patients showing very poor healing after RFA due to acidic irritation of the ablated mucosa, fundoplication may be necessary. 36,37 The best timing for fundoplication in relation to RFA treatment still needs to be studied.

9. Follow-up after endoscopic treatment of Barrett’s oesophagus
As described in chapter 4, 7 and 8, the majority of recurrences of IM and neoplasia occur at the gastro-oesophageal junction (GO-junction). 1,15,16 Eradication of all IM at this level should therefore be optimized. For SRER this implies that resections should extent deep enough into the cardia. Also, the entire circumference of the GO-junction should be resected, even in patients who only display tongues of Barrett’s mucosa. For RFA this implies that the entire circumference of the GO-junction should be treated at least once with the focal HALO device, since HALO ablation at this level is often insufficient due to poor contact between the electrode and the mucosa. Endoscopic differentiation between gastric mucosa and IM is almost impossible, making it difficult to judge if all Barrett’s mucosa has been eradicated. An endoscopically based endpoint for eradication of BO is therefore quite subjective. We have therefore used the criterion of histologically proven IM before treating patients with RFA, which enables us to use the objective endpoint of histological eradication of IM post-RFA. However, by using this endpoint, we do occasionally encounter a finding of focal IM in random biopsies obtained from the cardia during follow-up in patients who had already reached eradication of all Barrett’s mucosa. One may argue that residual IM in the cardia reflects incomplete cure of the underlying disease. However, IM of the cardia can be detected in up to 25% of patients with a normal appearing squamocolumnar junction and is not considered premalignant in those cases. 34 We therefore repeat endoscopic inspection and biopsies within one year in the case of non-dysplastic IM. In the case of LGIN, HGIN or cancer, however, additional treatment is necessary. The behavior of the neosquamous columnar junction after endoscopic therapy is unclear. In accordance with our findings, other groups have also reported on the issue of neoplasia developing in the cardia months to years after complete removal of BO. 35,36 During follow-up, this area should therefore be inspected thoroughly and biopsies should be obtained to assess for IM.

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As described above, a histological parameter is preferable over an endoscopic parameter during follow-up of the GO-junction post-RFA. However, for the nequosamous epithelium the opposite is the case: thorough endoscopic evaluation of the nequosamous epithelium for columnar mucosa is in our opinion more important than taking random nequosamous biopsies. Currently, a lot of attention during follow-up after RFA goes out to the presence of “buried Barrett’s”. However, as demonstrated in chapters 10 and 11, buried glands are very rare if the nequosamous mucosa looks normal upon endoscopic inspection. As described in chapter 11, we found a 0.1% rate of buried glands in over 2,500 biopsies from endoscopically normal nequosamous epithelium. However, when small islands of columnar mucosa were biopsied, buried glands were detected in 21% of biopsies. In addition, the cases of subquamous neoplasia we diagnosed in over 10 years (all occurring after complex treatment with PDT or APC) were all detected as endoscopically visible abnormalities. All these subquamous lesions could be treated endoscopically, referral for surgery was never needed and no patients died from this diagnosis. Therefore, after thorough endoscopic inspection the nequosamous epithelium with high-definition endoscopy and narrow-band imaging (NBI) to detect areas of columnar mucosa, random ‘blind’ biopsies of the nequosamous epithelium have little additional value.

In the future, endoscopic follow-up may consist of thorough endoscopic inspection of the nequosamous mucosa and GO-junction. Biopsies will only be obtained immediately distal to the GO-junction, and if necessary from any visible mucosal irregularities or columnar mucosa in the tubular oesophagus. If patients do not show recurrence of IM or neoplasia within the first year, endoscopic follow-up can be performed at longer intervals, or even omitted. EUS during follow-up may be reserved for those patients with risk factors for lymph node metastasis, such as submucosal invasion, poorly differentiated cancer, or lymph–vascular invasion in the diagnostic ER-specimen.

10. Training and centralization of Barrett’s management

Although new developments have made endoscopic treatment for Barrett’s neoplasia easier and accessible, it should be born into mind that ER and ablation are only technical parts of overall Barrett’s management. An endoscopist should also be able to recognize neoplastic lesions, and identify patients who are eligible for curative endoscopic treatment. Furthermore, adequate histological evaluation should be available, as well as surgical assistance in the case of failed endoscopic treatment or complications that cannot be managed endoscopically.

Structured training aimed at improvement of endoscopic detection, endoscopic treatment and histological evaluation of ER specimens is therefore necessary. The last couple of years, such training programs have successfully been set up in Europe (www.endosurgery.eu, www.rfa-academia.eu). By using a teaching-the-teachers model, these training programs have managed to spread structured training to other countries where endoscopic therapy was still little practiced. Since Barrett’s neoplasia is not a very prevalent disease, it is difficult to get enough exposure to keep learned techniques at an adequate level. Patients will only benefit from all new developments in the field of endoscopic resection and ablation, if they are treated in centers with multidisciplinary expertise and if endoscopic treatment is performed by a well-trained endoscopist. In the future, treatment of BO should therefore be centralized in dedicated centers.

REFERENCES


