Endoscopic management of Barrett’s esophagus with dysplasia
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The aim of this thesis was to optimize endoscopic management strategies for patients with Barrett’s esophagus containing dysplasia. To that end, we focused on patients with dysplasia throughout the entire spectrum: from early cancers and high-grade dysplasia to low-grade dysplasia patients. We examined the long-term results of endoscopic therapy, and we evaluated the effect of different endoscopic ablation regimens on our success rate in eradicating dysplastic Barrett’s mucosa. In low-grade dysplasia patients we investigated the role of the expert pathologist, and the effect of preventive ablation on the risk of neoplastic progression and its cost-effectiveness. In the following paragraphs we will discuss implications of this thesis for clinical practice and directions for future research.

**IMPLICATIONS FOR CLINICAL PRACTICE**

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*Treatment of high-grade dysplasia and early Barrett’s cancer*

**INDICATIONS FOR TREATMENT** Endoscopic techniques for curative treatment of early Barrett’s neoplasia (high-grade dysplasia and mucosal cancer) have substantially improved over the past decade. As a result endoscopic therapy is nowadays the standard of care over surgical treatment. Endoscopic resection (ER) for visible lesions, complemented with radiofrequency ablation (RFA) to remove the entire Barrett’s segment had already proven its efficacy and safety in a number of pilot studies.\(^1\)-\(^3\) The excellent long-term outcomes of this combined approach, as described in Chapter 3 and 4 of this thesis,\(^4\) support the use of endoscopic therapy as the primary treatment strategy for early Barrett’s neoplasia. Subsequently, this approach has been implemented in both national and international guidelines for the management of Barrett’s neoplasia.\(^5\)-\(^7\)

Although its efficacy and safety have been proven for high-grade dysplasia and mucosal cancer, there is debate if endoscopic therapy also has a place in the management of Barrett’s cancer infiltrating the superficial submucosa. Currently, surgical treatment is considered the gold standard for this subgroup of patients given the supposedly increased risk of lymph-node metastasis (LNM). In retrospective surgical series LNM has been reported in up to 50% of submucosal cancers. The risk of LNM appears to be much lower (0%-21%) in cancers limited to the most superficial one-third of the submucosa (sm1).\(^8\)-\(^13\) This has also been confirmed in studies where sm1 cancers with certain histological ‘low-risk features’ in the ER specimen carry a more favorable LNM pattern.\(^14,15\) Manner and coauthors and Alvarez Herrero and coauthors suggested the following criteria to define these ‘low-risk’ submucosal cancers; tumor invasion is limited to sm1 (<500µm), good to moderately differentiated cancers (G1-G2), absence of lymph-vascular invasion.\(^14,15\) In the first long-term series of sm1 patients with ‘low-risk’ lesions who were treated with endoscopic resection, Manner and coauthors reported an estimated overall 5-year survival rate of 84% and no tumor-associated deaths. LNM was found in one patient (1.9%) who was treated with curative esophagectomy (tumor free follow-up: 32 months).\(^16\) In the study by Alvarez Herrero and coauthors none of the twelve sm1 patients had LNM.\(^14\) Given that most patients with ‘low-risk’ sm1 cancers are elderly and often suffer from significant comor-
bidities, endoscopic treatment may be considered a safe and effective alternative to surgery in these cases.

TECHNICAL IMPROVEMENTS In this thesis we describe several practical improvements of the radiofrequency ablation protocol. The circumferential and focal ablation regimen as described in Chapter 3 and 4 have the disadvantage that several introductions of the endoscope and the ablation catheters are required to clean the electrode and ablation zone in between. This is uncomfortable for patients as the procedure is time consuming and it can be difficult to re-introduce the ablation catheter.

Based on the results as described in Chapter 5 we recommend to use a simplified-no cleaning regimen for circumferential balloon-based ablation in patients with an uncomplicated esophagus. This regimen consists of two consecutive applications of energy at 12J/cm² without the cleaning step in between. In patients with a more complex Barrett’s segment, i.e. due to a tortuous esophagus, extensive scarring at the ER site or relative stenosis, the cleaning step within the standard regimen may still be preferred to assess the completeness of the first ablation pass. In those patients the balloon may migrate during ablation resulting in skipped zones or zones with too much overlap. The cleaning step allows for adjustment of the balloon position during the second ablation pass.

In Chapter 6 we studied a simplified-no cleaning regimen for focal ablation of residual Barrett’s islands. This regimen consisted of three consecutive applications of energy at 15J/cm² without the cleaning step in between, and proved non-inferior to the standard regimen (2x2x15J/cm² with cleaning) for eradication of Barrett’s islands. In the past few years we have successfully used the simplified regimen for focal ablation of the whole Barrett’s segment in approximately 45 cases. In a retrospective analysis including our center and several others in the Netherlands, the simplified-no cleaning regimen appeared to be equally effective as the standard regimen for focal ablation of BE, including circumferential treatment of the gastro-esophageal junction. We were concerned that three consecutive applications might lead to deeper thermal damage resulting in more fibrosis and a higher rate of stenosis or other complications. Indeed, the observed stenosis rate (11%) was at the high end of the spectrum of stenosis reported in literature. In addition, 33% of these stenoses required ≥7 dilatations which suggests that these stenoses were more severe than observed in our earlier RFA studies. For these reasons, we have reduced the energy setting for focal RFA treatment from 15 to 12 J/cm² while adhering to three consecutive applications of energy (3x12J/cm², no cleaning). We feel that this is the best compromise between efficacy, safety and practicality, acknowledging that no data are currently available supporting this view.

MANAGEMENT OF WIDESPREAD LESIONS As described in Chapter 4, the combined approach of ER followed by RFA is safe and effective for eradication of neoplastic Barrett’s esophagus, provided that the extent of the ER is limited to 2 centimeters in length and 50 percent of the circumference. In the preceding EURO-I study in which more widespread ER was allowed, the rate of mucosal lacerations after RFA and the rate of esophageal stenosis were far higher than in the EURO-II study. After extensive ER, scarring and stenosis are common, which may result in lesser electrode contact or superficial mucosal lacerations during RFA. However, in some patients widespread resection is unavoidable to completely remove mucosal irregularities as to render the mucosa flat for ablation and to ensure optimal histological staging.
For patients who require widespread ER an individual and tailored management strategy is required. Different endoscopic approaches are available as also described in Chapter 1 and 2: 1) The standard combined approach of ER followed by RFA, complemented with dilatation sessions after ER if necessary, 2) Stepwise radical endoscopic resection (SRER), 3) RFA and ER combined in a single treatment session. 4) Endoscopic submucosal dissection (ESD). Depending on the length of the original Barrett’s segment and the required extent of the endoscopic resection one of these approaches can be chosen and discussed with the patient. With the SRER technique the whole BE segment is removed in subsequent ER-sessions. Despite the excellent eradication rates achieved with this technique, it is associated with a much higher rate of stenosis when compared with ER plus RFA. SRER is a complicated technique and its use is generally restricted to patients with a BE <5 centimeters.18 The single-step approach, consisting of ER and circumferential ablation in one session, has proven feasible in expert hands, although the rate of complications was substantial.19 Alternatively, ER may be combined with focal ablation, which can be suitable for patients with widespread lesions in shorter segments of BE as the entire Barrett’s segment can be treated in a single session. For larger surface areas of Barrett’s mucosa the single-step approach using circumferential ablation would be more appropriate. Endoscopic submucosal dissection holds the advantage over other techniques that a large en-bloc resection can be obtained for adequate histological assessment. This can be particularly important in bulky lesions that cannot be captured in the cap or lesions suspicious of submucosal ingrowth, where ESD may ensure a better specimen for histological assessment than piecemeal ER (Figure 1). ESD is, however, a highly complex technique that requires extensive training. The experience with ESD in the western world is limited, due to the low caseload and the long learning curve. In our opinion ESD currently has a limited role in the treatment of early BE neoplasia.

Figure 1 Endoscopic images from patients with lesions suspected of a higher risk of lymph node metastasis.

The left and mid panel show a bulky lesion in a short Barrett’s tongue in forward view (left panel) and retrograde view (mid panel). In this patient ESD was performed for primary staging, the resection specimen showed submucosal invasion (sm) and focal vaso-invasive growth. This patient subsequently underwent esophagctomy, no residual cancer and no positive lymph nodes were detected in the resection specimen.

The right panel shows a lesion located at the gastro-esophageal junction which was suspected of submucosal ingrowth. ESD was chosen as the primary management strategy because this patient suffered from other comorbidities and depended on hemodialysis. Histopathology showed HGD with no invasive growth, the residual BE segment was subsequently treated with RFA.
MANAGEMENT OF POOR RESPONDERS TO RFA TREATMENT  Poor response after RFA occurs in a small subset of patients. These patients are generally identified early on during the treatment course: they demonstrate little regression of the BE segment or show persistent inflammation three months after their first circumferential therapy. Poor responders should not be confused with patients who require some form of escape therapy for residual BE after RFA. Whereas in true poor responders pursuing endoscopic treatment is generally futile, escape treatment is usually highly effective in patients who have undergone multiple ablations (generally one circumferential ablation and 2-3 focal RFA sessions) yet have some residual BE. Generally this is <10% of the original BE and often the escape treatment is chosen for its effectiveness and low costs knowing that the finish line is nearby. Endoscopic resection can be used for larger areas of residual BE whereas argon plasma coagulation is very useful for small islands or areas <5mm. Continuation of treatment until all Barrett’s mucosa is eradicated both visibly and histologically should be pursued to ensure low recurrence rates of neoplasia during follow-up. In this sense, endoscopic resection, radiofrequency ablation and argon plasma coagulation are complementary techniques for treatment of Barrett’s neoplasia.

Recently our group investigated potential predictors for poor initial response (defined as <50% regression after the first circumferential ablation), in a large multicenter cohort. Active reflux esophagitis, regeneration of the endoscopic resection site with Barrett’s epithelium (instead of squamous regeneration), esophageal narrowing pre-ablation, and the number of years with neoplasia before the first ablation session were found to predict a poor initial response and patients with these factors ultimately had a worse chance of reaching complete eradication of BE.

Since the presence of active reflux esophagitis under aggressive proton pump inhibitor (PPI) therapy predicts a poor outcome of endoscopic ablation, we advise to postpone endoscopic treatment until acid suppression therapy is optimized in such patients. In all our treatment protocols patients are prescribed double-dose maintenance PPI therapy. In our center we refer patients with a poor response on RFA or with active reflux esophagitis under PPI therapy for pH monitoring on PPI therapy to determine whether PPI therapy can be further optimized. Poor responders who do not respond to optimal medical therapy can be referred for Nissen fundoplication before endoscopic treatment is continued. It should be kept in mind that if future esophageal surgery is necessary for cancer treatment this may be hampered by fundoplication.

Regeneration of the ER scar with Barrett’s epithelium may suggest early on that these patients have a reduced ability to re-epithelialize with normal squamous epithelium. Depending on the patient’s age and the severity of dysplasia one can opt for keeping such patients under strict endoscopic surveillance and to perform endoscopic resection only for visible lesions.

In patients with esophageal narrowing before ablation (i.e. by reflux esophagitis or endoscopic resection), optimal ablation can be hampered in two ways. First, these patients may belong to a subgroup of patients with more severe reflux than others, which is likely to induce reflux-related scarring. In these patients acid suppression should be optimized, as described previously, before endoscopic treatment is continued. Second, any stenosis may result in suboptimal contact between the electrode and the mucosa leading to less effective ablation. Dilating before the next ablation session may optimize electrode contact. In such cases we continue dilatation sessions on a weekly basis until the esophagus has an inner diameter of 18-mm
and passage of an 18-mm bougie does not cause mucosal damage. We feel that
dilatation and balloon-based ablation should not be combined in the same session.
For selected patients who have a combination of the aforementioned predictors for
a poor response to RFA, a primary surgical approach should be considered, even
though the BE may “only” harbor high-grade dysplasia and mucosal cancer. For in-
stance in a young patient with a BE>C10M10, a pre-treatment narrowed esophagus,
poorly controlled reflux disease under high-dose PPI, widespread visible lesions
with multifocal neoplasia, and prior scarring due to ulceration.

ENDOSCOPIC FOLLOW-UP AFTER TREATMENT In our clinical studies on radio-
frequency ablation and endoscopic resection we have used strict endoscopic
follow-up protocols, with endoscopies scheduled twice in the first year and annually
thereafter, while obtaining extensive random biopsies from neosquamous epithelium
and the gastro-esophageal junction. After successful eradication of neoplastic
Barrett’s esophagus, however, one might question the need for such an intensive
surveillance protocol.

Our initial reasons for performing such an extensive biopsy protocol during
follow-up examination were two-fold: First, there was a generally held concern
that occult buried glands might persist underneath neosquamous epithelium, thus
remaining endoscopically invisible while progressing to an advanced malignant
stage. The presence of buried glands had previously been reported in up to half
of patients treated with photodynamic therapy or argon-plasma coagulation as stand-alone treatment. More recent data of over 700 patients treated with RFA,
however, demonstrate that the rate of buried glands appears almost negligible. In
Chapter 3 and 4, buried glands were found in a total of 4 out of 7,717 biopsies,
(corresponding to a rate of 0.05%). Studies have shown that biopsy depth of treated
and untreated squamous epithelium is similar, hence neosquamous biopsies are of
adequate depth to evaluate the presence of buried glands. Furthermore, biopsies
obtained close to the gastro-esophageal (GE) junction or accidental sampling of re-
sidual Barrett’s mucosa can lead to a false-positive diagnosis of buried glands. The
results as described in this thesis demonstrate that the presence of buried glands
in normal appearing neosquamous epithelium is rare. This is also illustrated by two
studies from our group in which ER specimens were obtained from neosquamous
epithelium in 44 patients who had complete endoscopic conversion of their BE
after RFA. In none of 44 ER specimens buried glands were detected whereas exten-
sive submucosal tissue was present in each sample.

The second reason for performing an extensive biopsy protocol during follow-
up examinations is that several studies have demonstrated that the GE junction is
the area most at risk for recurrence of neoplasia. A reliable endoscopic tool
to predict if all Barrett’s mucosa has been eradicated at this level is not available.
Even endoscopic detection techniques such as narrow-band imaging have not been
able to aid the endoscopist in the differentiation between gastric mucosa and IM.
As a result we always obtain biopsies immediately distal to the GE junction as an
objective endpoint for eradication. The downside of this biopsy protocol is that
it can lead to detection and overestimation of non-dysplastic IM in the presence
of a normal appearing GE junction on endoscopy. In patients who have undergone
endoscopic therapy for Barrett’s neoplasia, subsequent detection of IM in the cardia
either reflects insufficient treatment of that area, truly recurrent disease, or an
irrelevant normal finding. As described in Chapter 3 and 4, in most cases where IM
of the cardia is observed during follow-up, IM is only detected in a single biopsy: the diagnosis is generally not reproduced during follow-up examination, and this “single hit IM” shows no increased incidence over time. This suggests that IM found in the cardia during follow-up examination does not reflect residual BE (since the detection of IM should then be reproduced over time) or recurrent disease (since its incidence should then increase with the duration of follow-up). Studies have shown that IM is found in up to 25% of the normal population in this area, and this is generally not considered a pre-malignant condition. Therefore, the presence of IM in the cardia during follow-up examination seems of limited clinical relevance.

Based on the results as described in this thesis we therefore propose several changes to the endoscopic follow-up protocol. As described in Chapter 1, the cornerstone of endoscopic follow-up should consist of meticulous endoscopic inspection of the neosquamous mucosa and the GE junction, to rule out the presence of residual columnar mucosa. This can be achieved using high-resolution endoscopy with narrow-band imaging, performed by an endoscopist with a trained eye. The need to obtain random biopsies from the neosquamous mucosa has become obsolete given the low rate of buried glands. While meticulous inspection is performed it is sufficient to obtain targeted biopsies only, in case of visible lesions or of areas of residual columnar mucosa. If small Barrett’s islands (<5mm) are detected during follow-up examination these can best be treated with argon-plasma coagulation (APC) instead of biopsied, as this can lead to a false-positive diagnosis of buried glands. Moreover, biopsying is an irradical treatment modality if a biopsy would prove to be positive for dysplasia. Because it is often impossible to re-detect such small areas on endoscopy, immediate APC should be performed.

Obtaining biopsies immediately below the GE junction remains important, given that this is the most important region at risk for recurrence. If IM is found in this region we advocate to repeat focal ablation only when IM is detected at the first follow-up endoscopy, subsequent touch-up ablation during follow-up is unnecessary when dysplasia is absent. Given the irrelevance of IM of the cardia during follow-up one may even question the relevance of obtaining cardia biopsies in patients with a normal appearing GE junction, after consecutive follow-up endoscopies have shown absence of IM in this area.

After successful eradication of neoplastic Barrett’s esophagus, we propose to perform the next follow-up endoscopy after 6 months and annually thereafter. This means that follow-up endoscopies are performed at 3 months (when biopsies show absence of dysplasia and IM), 9 months (6 months interval) and 21 months (12 months interval) after the last treatment. The few neoplastic recurrences that occur, can then be detected at an early stage during follow-up and can easily be managed endoscopically.

WHO SHOULD DO THE TRICK? Following the developments in surgery, where many procedures are subject to volume standards, recent international guidelines have recognized the importance of centralization of treatment for Barrett’s neoplasia. This is mainly driven by the better outcomes of endoscopic therapy in high-volume centers. Besides the concentration of endoscopic treatment in dedicated centers with an adequate case-load, management of patients with Barrett’s esophagus with neoplasia also requires a multimodality approach. The endoscopist should be trained in the detection of neoplastic lesions, selection of patients for treatment, and the technical aspects of endoscopic treatment. This should be combined with
adequate histologic evaluation of specimens by an expert pathologist. Surgery should be available as a back-up for complications of endoscopic treatment or in case esophagectomy is necessary. A structured training program aimed at ‘imaging’ to improve endoscopic detection, ‘treatment’ to teach the technical aspects of endoscopic resection and ablation, and ‘pathology’ to teach histological evaluation of specimens, has been made available to endoscopists and pathologists at our center and elsewhere in Europe (www.best-academia.eu).

For the large multicenter studies described in Chapter 3 and 8 endoscopists and pathologists were trained according to this principle. We believe that training can achieve a high procedural success rate of endoscopic resection and radiofrequency ablation. We therefore recommend that future national guidelines include standards (i.e. training, volumes, etc) that should be met, before a center can offer endoscopic treatment of neoplastic BE. Developing expert pathology panels is an essential parallel development to the centralization of endoscopic treatment.

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**Low-grade dysplasia in Barrett’s esophagus**

A PARADIGM SHIFT  Given the excellent results of radiofrequency ablation (with or without primary endoscopic resection) for the eradication of neoplastic Barrett’s esophagus, our research focus gradually shifted towards the optimal management strategy for low-grade dysplasia as described in Part 2 of this thesis.

Low-grade dysplasia in Barrett’s esophagus has been surrounded by uncertainties regarding the diagnosis and the natural history of the disease. Several studies suggested that low-grade dysplasia does not carry an increased risk of neoplastic progression compared with non-dysplastic Barrett’s esophagus, or claimed that the absolute risk is only marginally increased. These studies, however, lacked expert pathology review or had strikingly poor inter-observer agreement between pathologists. Three independent studies by our group, including those described in Chapter 7 and 8, have demonstrated that biopsy review by a Dutch expert pathology panel will downgrade the majority of community low-grade dysplasia diagnoses to non-dysplastic BE with a very low risk for neoplastic progression. Patients with a confirmed diagnosis of low-grade dysplasia, however, have a risk of neoplastic progression of 9.1%-13.4% per person-year.

Studies from the United States have used radiofrequency ablation for low-grade dysplasia. Shaheen and coauthors and Sharma and coauthors demonstrated that ablation can achieve eradication of Barrett’s esophagus with low-grade dysplasia in 81% to 90%, and 90% to 100% of cases, respectively.

Based on these data, we initiated a randomized clinical trial (SURF) among patients with a confirmed diagnosis of low-grade dysplasia by an expert panel of pathologists as described in Chapter 8. In this trial we compared standard endoscopic surveillance (control) with radiofrequency ablation (ablation) in their effect on neoplastic progression. The results from this trial suggested that ablation reduces the risk of neoplastic progression with 25%, corresponding to a number needed to treat of 4.0. Furthermore, ablation was able to reduce the risk of progression to adenocarcinoma with 7.4%. We achieved eradication rates of low-grade dysplasia and Barrett’s esophagus of 93% and 88%, respectively.
To be eligible for the SURF trial only a single diagnosis of LGD was required. As a result, in 28% of patients in the control group no dysplasia was detected during follow-up examinations. Other studies have reported similar rates for not reproducing the LGD diagnosis over time: Shaheen and coauthors reported clearance of dysplasia in 26% of LGD patients at 12 months follow-up. In Chapter 9 we demonstrated that ablation for low-grade dysplasia is potentially cost-effective, but avoiding ablation in patients without dysplasia may even further improve the cost-effectiveness profile of ablation. Although no data are currently available supporting this view, insisting that a diagnosis of low-grade dysplasia is not only confirmed but also stable over time may improve the selection of patients. This assumption was incorporated into the cost-effectiveness modeling study by Hur and coauthors, and their study suggested that ablation can be cost-effective provided that the diagnosis of LGD is confirmed and stable. In addition, an increasing number of publications on the long-term efficacy show that ablation is durable in more than 90% of patients during follow-up, and that the risk of progression in these patients is small. Ongoing surveillance after successful ablation of low-grade dysplasia is therefore of limited value, and stopping surveillance or expanding surveillance intervals will further improve the cost-effectiveness of ablation.

The results from the SURF trial have induced a paradigm shift in our management of patients with Barrett’s esophagus and low-grade dysplasia. Instead of routing for endoscopic surveillance at an increased interval (every 6 to 12 months) we believe that the preventive effect of ablation is favorable after optimal selection of patients. The first step should always include review of the low-grade dysplasia diagnosis, preferably by an expert pathology panel. Once the diagnosis has been confirmed, we advocate that low-grade dysplasia has to be reproduced on more than one occasion before treatment is initiated. After successful ablation we advocate to perform a follow-up endoscopy 12 months after the last treatment session, if no intestinal metaplasia is detected surveillance can be stopped.

WHAT DEFINES AN “EXPERT PATHOLOGIST”? A general development in medical practice in the Netherlands is the centralization of healthcare and the concentration of medical procedures among “experts” in the field. Parallel to the focus on the “expert endoscopist” in the first part of this thesis, we have focused on the “expert pathologist” in the second part of this thesis. We have demonstrated that a panel of expert pathologists can accurately risk-stratify patients with low-grade dysplasia. To extrapolate the results of this thesis into clinical practice, it would be important to know who should be considered an “expert pathologist”. Several guidelines have stipulated that the diagnosis of Barrett’s esophagus with dysplasia should at least be evaluated by two experienced pathologists in the field or two gastro-intestinal pathologists. However, none of these guidelines provide criteria to define “expert pathologist”. The expert pathologists that we have consulted for the studies described in this thesis were considered as such by their (international) peers. All of our pathologists are dedicated to the field of Barrett’s by a high exposure or case-load (approximately 5-10 cases per week). Future experts may be trained in recognition of dysplasia and neoplastic lesions according to the BEST academia training program (www.best-academia.eu). Development of an online platform and training module are currently underway. Ideally, a benchmark exam based on the training module could be used for qualification as an expert pathologist.
IS TREATMENT OF NON-DYSPLASTIC BARRETT’S ESOPHAGUS THE NEXT STEP?

As opposed to low-grade dysplasia, where certain patients can benefit from ablation as shown in Chapter 8 and 9, endoscopic ablation does not appear to be a cost-effective approach for non-dysplastic Barrett’s esophagus. This is mainly due to the poor ability to risk-stratify non-dysplastic BE patients into low and high risk patients, as a result the overall risk of progression of non-dysplastic BE is much lower than for low-grade dysplasia. Nevertheless, certain non-dysplastic BE patients may have a personal risk profile for progression. These selected cases, i.e. with a family history of esophageal adenocarcinoma, younger than 50 years with a long life-expectancy, or a long Barrett’s segment, can be referred to an expert center for endoscopic surveillance. Depending on patient and endoscopist preference, ablation can then be considered. In general, however, endoscopic treatment is not the preferred standard of care for patients with non-dysplastic BE. It should be noted that only few non-dysplastic BE patients meet the aforementioned arbitrary criteria.

IMPLICATIONS FOR RESEARCH

The results of this thesis have particular implications for research in the field of low-grade dysplasia. In Chapter 7 and 8 we demonstrate that if an expert panel of pathologists at least moderately agrees on the diagnosis of low-grade dysplasia, the risk of neoplastic progression in case of a confirmed diagnosis is substantial. The diagnosis of low-grade dysplasia is difficult and fraught with uncertainties related to the natural course of the disease. Many previous studies in the field that reported progression rates for patients with low-grade dysplasia, suffered from a lack of expert histologic review or poor inter-observer agreement. In these studies the reliability of the low-grade dysplasia diagnosis is questionable, which likely has resulted in the wide variability in reported progression rates.

We show that in the majority of patients with a community low-grade dysplasia diagnosis, reactive inflammatory changes are often misinterpreted as such. As a result most of these cases can be downgraded by an expert panel of pathologists and these patients have a low risk of neoplastic progression. In those patients in whom the diagnosis is confirmed by an expert panel, the annual risk of neoplastic progression is 9.1%-13.4% per person-year. This shows that accurate risk-stratification of patients with low-grade dysplasia is possible by a properly trained and interacting expert panel. Future studies on low-grade dysplasia should therefore incorporate expert pathology review and report the inter-observer agreement amongst the panel pathologists.
An important question is whether indications for endoscopic treatment can be expanded beyond mucosal and ‘low-risk’ submucosal cancers. A promising therapeutic approach has been developed by our group and consists of endoscopic radical resection of the lesion (either by ESD or ER), followed by thoracolaparoscopic lymph node dissection without concomitant esophagectomy. Pilot studies in swine and human cadavers have shown the feasibility and safety of this procedure. Future studies will be necessary to determine whether this approach can have a place in the management of patients with ‘high-risk’ submucosal Barrett’s cancers.

With regards to patient-comfort during treatment, the developments in endoscopic technique have significantly improved patient care. Certain vital aspects remain to be studied in the future. First, the introduction of the ablation balloon and the focal device remain uncomfortable even though we have partly succeeded in optimizing the ablation regimen (less introductions of endoscope and devices). Studies on the safety and efficacy of a self-sizing balloon device are currently underway. This device has the advantage that it avoids the sizing step for circumferential ablation procedures, thus reducing the number of introductions. In addition, the simplified focal ablation regimen can be improved further by re-evaluating energy settings. In Europe the focal device has been mainly used at 15J/cm², both for the standard and simplified regimen. Lowering the energy density to 12J/cm² (in accordance to the US standard protocol) when using the simplified triple-application may reduce the risk of fibrosis and stenosis even further. Second, strategies to prevent esophageal stenosis after (extensive) endoscopic resection may reduce the need for subsequent dilatations. In this thesis we describe stenosis rates after treatment in up to 11% of patients. In studies in which more than 75% of the circumference is resected, the rate of stenosis increases to 90%. Different strategies have been studied in animal models and humans to prevent stenosis formation: by covering or reconstructing the ER wound (i.e. transplant tissue-engineered cell sheets), by preventing inflammation at the ER site (botulin or steroid injection, administration of non-steroidal anti-inflammatory drugs) or by mechanical prevention using balloon dilatation or esophageal stents. None of these concepts have thus far been able to adequately prevent the development of stenosis in humans. Future studies should be directed toward a better understanding of wound healing and the subsequent formation of stenosis.

As shown in this thesis RFA has not only proven safe and effective for eradication of Barrett’s neoplasia, but eradication has also proven durable in the long-term, while minimizing the known drawbacks of photodynamic therapy and argon plasma coagulation, such as buried Barrett’s glands. Drawbacks of RFA treatment are the relatively high costs of the ablation devices and several practical limitations as mentioned in the previous paragraph (i.e. multiple introductions of the devices, stenosis rate). Argon-plasma coagulation (APC) has been studied as a cheaper alternative, and has shown to be effective and easily accessible. However, when compared to RFA limited data are available on APC, and the few small series reported stenosis rates in up to 15% of patients. For treatment of an entire BE segment APC is currently not the most practical technique: it is an operator-dependent technique and has to be performed spot-by-spot making it time consuming for...
ablation of larger areas. As mentioned previously we often use APC as patch-up treatment for residual islands or small BE areas <5mm as a cheaper alternative to focal RFA at the end of the treatment phase. Recently the Hybrid-APC technique has been introduced, which combines a central water channel for submucosal fluid injection (based on the waterjet technology) and a gas channel for the APC function in a single probe. By injecting a solution such as 0.9% potassium chloride into the submucosa it is hypothesized that the depth of thermal injury can be reduced in order to prevent stenosis after APC. Hybrid-APC may be an attractive technique for ablation of smaller surface areas of BE such as tongues or the squamocolumnar junction. To be considered a valid alternative to RFA, however, Hybrid-APC needs to be able to achieve similar eradication rates as RFA without being associated with stenosis rates as in previous APC studies. A European multicenter study evaluating Hybrid-APC as the primary ablation therapy for the eradication of dysplastic BE is currently underway.

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**Low-grade dysplasia in Barrett’s esophagus**

The largest unsolved question in this field is how to diagnose low-grade dysplasia objectively, and subsequently how to risk-stratify patients into low-risk and high-risk categories. The more ‘purified’ a low-grade dysplasia cohort is, the higher the risk of progression and the higher the net health benefit of an intervention such as endoscopic ablation will be. In our view, future basic research focusing on low-grade dysplasia should be directed to two main pillars: optimizing the diagnosis of low-grade dysplasia and searching for biomarkers.

**OPTIMIZING THE DIAGNOSIS** We already demonstrated that biopsy review by an expert panel with a high inter-observer agreement leads to a better histological risk-stratification of low-grade dysplasia. In the SURF trial we identified clinical predictors for progression such as the number of years since the diagnosis of Barrett’s esophagus, the number of endoscopies with dysplasia before inclusion and circumferential Barrett’s length in centimeters. Unfortunately, our multivariable analysis could not identify clinical predictors for absence of low-grade dysplasia during follow-up.46

We are currently developing a predictive model based on the histological diagnosis of 375 patients screened for the SURF trial. The histological slides are reviewed separately by 3 expert pathologists, who will evaluate each available level of biopsies from the BE segment. Endoscopic and histological follow-up data are retrieved for all patients (including those excluded from enrollment in the SURF trial), to determine the rate of neoplastic progression during follow-up among the whole cohort screened for the study. This research will aim to identify the relation between spatial and temporal distribution of a diagnosis of low-grade dysplasia and the extent of agreement between expert pathologists for the diagnosis of low-grade dysplasia with the subsequent risk of progression. Combining these histological features with the previously identified clinical predictors may result in a model that will likely aid in the selection of low-grade dysplasia patients for ablation in the future.
THE SEARCH FOR BIOMARKERS  Ideally, the subjective histological assessment should be replaced by a panel of molecular biomarkers that are able to objectively identify patients who carry a low or high risk of neoplastic progression. Such a risk stratification will greatly improve the cost-effectiveness of endoscopic surveillance, as unnecessary endoscopies can potentially be avoided in the low-risk group, whereas high risk patients may undergo prophylactic eradication of their Barrett’s esophagus.46,42

Research on potential biomarkers for neoplastic progression includes markers of DNA content abnormalities, abnormalities in p53 and p16 tumor suppressor genes, clonal diversity, and epigenetic changes.63,64 Although potential biomarkers have been identified in retrospective studies, none of these biomarkers are ready for clinical practice yet. To achieve this, prospective validation studies are required to evaluate the impact of a biomarker test on population disease burden, with primary outcomes including costs and mortality.65

In the past years we have developed the ReBus biorepository, a collection of human biospecimens (biopsies, cytology, serum, etc) obtained from patients with a diagnosis of Barrett’s esophagus. These patients were recruited from community and academic hospitals within the Amsterdam region. Recently, two different biomarker panels were tested within this cohort (biopsies and brush cytology). The panel consisting of cyclin A, Aspergillus oryzae lectin and p53 tested in biopsies was able to predict progression to esophageal adenocarcinoma.66 The panel using fluorescence in situ hybridization in cytology samples showed ability for risk-stratification among non-dysplastic Barrett’s patients.67 These promising results hopefully give rise to future prospective validation studies.

WHAT DO PATIENTS WANT? Even if selection of patients with low-grade dysplasia can be optimized, true patient preferences remain unknown. Quality of Life data of the SURF trial indicate that patients are less concerned and view their disease as less threatening when they undergo ablation instead of endoscopic surveillance.51 A preference study among non-dysplastic Barrett’s patients showed that endoscopic intervention is often preferred over chemoprevention, although a proportion of patients had no preference for either strategy. Importantly, the authors showed that even under optimal circumstances, patients may still refute endoscopic interventions.48 Studying preferences and shared-decision making processes among patients with low-grade dysplasia may elucidate which factors drive patients for one or the other strategy, and may be the final step in improving clinical practice.68,69
Endoscopic management of Barrett’s esophagus with dysplasia is shifting toward earlier therapeutic interventions instead of surveillance. For high-grade dysplasia and early cancer, endoscopic resection for removal of visible lesions followed by radio-frequency ablation to eradicate the residual Barrett’s epithelium is considered the treatment of choice. This combined approach has proven durable with a low rate of neoplastic recurrences during long-term follow-up. Radiofrequency ablation is now also indicated for selected patients with low-grade dysplasia, as ablation greatly reduces the risk of neoplastic progression at an acceptable cost-profile, while altering patients’ illness perception. Future research should focus on improving patient care, by further optimizing ablation regimens, evaluating new devices, finding ways to prevent formation of stenosis after endoscopic therapy, and studying patient preferences. Much remains to be gained in objectifying the diagnosis of low-grade dysplasia and the subsequent risk-stratification of patients to improve the net health benefit of preventive ablation.


59. Barret M. “Mucosal repair after endoscopic procedures in the esophagus: from scar formation to stricture prevention”. Seminars in Gastroenterology and Hepatology. Academic Medical Center Amsterdam, Amsterdam. 11 June 2014. Lecture.


