Endoscopic therapy of Barrett's esophagus

Oliver Pech and Christian Ell

Department of Internal Medicine 2, HSK Wiesbaden, Wiesbaden, Germany

Correspondence to Oliver Pech, MD, PhD, Department of Gastroenterology, HSK Wiesbaden, Ludwig-Erhard Street 100, 65199 Wiesbaden, Germany
Tel: +49 611 432420; e-mail: oliver.pech@t-online.de

Current Opinion in Gastroenterology 2009, 25:000–000

Purpose of review

Endoscopic therapy for early neoplasia arising in Barrett's esophagus has gained wide acceptance in the USA and Europe, and long-term results of endoscopic resection and photodynamic therapy and new ablation techniques are available now. This review summarizes the different indications for endoscopic treatment and the recent data on the different endoscopic treatment techniques.

Recent findings

Endoscopic treatment of high-grade intraepithelial neoplasia has proven to be well tolerated and effective even after a long-term follow-up of more than 5 years. Radiofrequency treatment seems to be an effective technique for ablation of Barrett's esophagus with low and high-grade intraepithelial neoplasia on short-term follow-up with a very low complication rate. Recent data were able to demonstrate that biomarkers can predict the treatment effect of photodynamic therapy and several risk factors for stricture formation after treatment could be identified.

Summary

Endoscopic therapy of early Barrett's neoplasia has proven to be well tolerated and effective and can be considered as the treatment of choice for most patients with this disease. Visible lesions should be treated by endoscopic resection in order to obtain a specimen for histological work up. The remaining nondysplastic Barrett's epithelium after complete resection of all neoplastic lesions should be ablated, for example, by radiofrequency treatment, to prevent metachronous or recurrent neoplasia.

Keywords

adenocarcinoma, Barrett's esophagus, endoscopic resection, photodynamic therapy

Curr Opin Gastroenterol 25:000–000

0267-1379

Introduction

In recent years, increasing attention has focused on adenocarcinoma arising in Barrett's esophagus, mainly because of the dramatic increase in the incidence of the disease. Recent publications have reported that the incidence of cancer in Barrett's esophagus has risen approximately six-fold in the United States. Esophageal adenocarcinoma is now even more frequent than esophageal squamous cell cancer in Western countries [1].

The development of carcinoma is causally linked to gastroesophageal reflux disease, probably passing through premalignant stages known as Barrett's metaplasia, low-grade intraepithelial neoplasia (LGIN), and finally high-grade intraepithelial neoplasia (HGIN) [2,3]. Because of increasing awareness of this causal link among physicians, carcinoma in Barrett's esophagus is being identified more often at an early stage, particularly in patients who are receiving surveillance [4,5].

The appropriate management of patients in whom early carcinoma or HGIN has been detected continues to be a subject of controversy. For many years, radical esophageal resection has been regarded as the treatment of choice, but because of the high morbidity and mortality rates associated with the procedure, less radical treatment strategies have been advocated by many groups [6].

Indications for endoscopic therapy

The choice of the treatment method in patients with Barrett's esophagus is highly dependent on the different stages of the disease. Table 1 illustrates the different treatment recommendations.

Barrett's epithelium without neoplastic changes

The risk of developing HGIN or adenocarcinoma in nondysplastic Barrett's esophagus is very low. Several studies [7–9] have reported a risk of about 0.5% per patient-year. As adenocarcinoma in Barrett's esophagus seems to develop over several stages and because cohort studies showed that most patients with Barrett's esophagus do not progress past nondysplastic Barrett's esophagus, most national guidelines recommend a conservative

Table 1 Treatment strategy of Barrett's esophagus according to the grade of neoplasia

Histological grade	Recommended treatment
Barrett's esophagus without neoplastic lesions	Surveillance endoscopies with high-resolution endoscopes, advanced imaging techniques and four-quadrant biopsies
Barrett's esophagus with visible/localizable LGIN	Confirmation of the histological diagnosis by an expert gastrointestinal pathologist should be obtained Endoscopic resection of all visible lesions
Barrett's esophagus without visible LGIN	Surveillance endoscopies with high-resolution endoscopes, advanced imaging techniques and four-quadrant biopsies according to national guidelines Ablative treatment in prospective studies
Barrett's esophagus with HGIN	Endoscopic resection of all neoplastic lesions Ablation of the remaining nondysplastic Barrett's epithelium
Barrett's esophagus with mucosal adenocarcinoma	Endoscopic resection of all neoplastic lesions Ablation of the remaining nondysplastic Barrett's epithelium
Barrett's esophagus with submucosal adenocarcinoma	Esophageal resection recommended Endoscopic resection of adenocarcinoma invading only the upper third of the submucosal layer (pT1sm1) in expert centers

HGIN, high-grade intraepithelial neoplasia; LGIN, low-grade intraepithelial neoplasia.

management of these patients with periodic surveillance endoscopies every 2–3 years [10–13].

However, a recent meta-analysis [14] was able to demonstrate that the cancer risk in patients with nondysplastic Barrett's esophagus could be reduced by ablative treatment from 5.98 per 1000 patient-years to 1.63 per 1000 patient-years.

Despite these data, ablative treatment of nondysplastic Barrett's esophagus is not indicated outside prospective studies for several reasons. First, the already mentioned very low cancer risk does not justify any treatment associated with a risk for the patient. Second, until now, there is no ablation technique available providing 100% ablation of Barrett's epithelium. Finally, so far there is no proof that ablation of Barrett's epithelium can eliminate the risk of progression and, therefore, periodical surveillance would probably still be necessary.

Barrett's esophagus with low-grade intraepithelial neoplasia

In individuals with LGIN, progression to HGIN is observed in between 6 and 28% [2,3,15]. However, a major difficulty with LGIN is its correct histological diagnosis. Very often regenerative changes are overdiagnosed as LGIN and therefore a second opinion by an expert gastrointestinal pathologist should always be obtained [16]. In a study from our group, histological slides of 50 patients with the referral diagnosis of LGIN were checked by two independent expert pathologists, and 50% of LGIN diagnoses were considered as not correct [16]. An overdiagnosis was made in 42% and an underdiagnosis was made in 8% (one HGIN and three adenocarcinomas).

There is an ongoing debate whether endoscopic treatment in patients with LGIN should be carried out or whether follow-up endoscopies are sufficient. In our opinion, when the diagnosis of LGIN was confirmed by an expert gastrointestinal pathologist and the lesion is localizable/visible, diagnostic endoscopic resection should be carried out, as LGIN is often contiguous to lesions with higher grades of dysplasia. However, in many cases, LGIN cannot be relocalized. In those cases, both follow-up endoscopies or ablative treatment can be performed. Up to now, there is no prospective randomized trial comparing both strategies in patients with LGIN.

Barrett's esophagus with high-grade intraepithelial neoplasia or adenocarcinoma

Patients with HGIN harbor an increased risk of the disease progressing to cancer with yearly rates of 2.2–11.8% [3,15,17] and endoscopic ablations seems to be able to reduce the rate of cancer progression from 65.8 to 16.76 per 1000 years [14]. In addition, HGIN is very often located next to cancer lesions, and adenocarcinoma is diagnosed in the resected specimen after endoscopic resection or surgery in up to 40% and very often represents the same lesion. For these reasons, endoscopic treatment for Barrett's esophagus with HGIN should be performed.

Mucosal Barrett's cancer is also an indication for endoscopic treatment. It has been shown that there is almost no risk of lymph-node metastasis in patients with adenocarcinoma limited to the mucosal layer (T1m1–4) and therefore endoscopic treatment can be considered to be curative in these lesions [18–20,21•].

Limitations for endoscopic treatment of early Barrett's cancers should be:

(1) submucosal infiltration [6] or
(2) lymph vessel (L1) [6] or
(3) venous infiltration (V1) [6].

Whether cancers limited to the upper submucosal layer (sm1) are eligible for endoscopic resection in selected cases is not as yet clear. Surgical series have been able to show that patients with sm1 Barrett's cancer have a very low risk of metastatic lymph nodes, but larger series reporting on the endoscopic treatment of these patients are still lacking [18,19]. A recently published series from our department could demonstrate that endoscopic resection seems to be well tolerated also in patients with low-risk submucosal cancer (T1sm1, G1–2, L0, V0, macroscopic type I or II): 21 patients were treated by endoscopic resection [22]. One patient was referred to surgery and one patient died (not tumor-related) before complete remission could be achieved. Eighteen out of 19 patients achieved complete remission after a mean of 2.9 endoscopic resections and 5.3 months. After a mean follow-up of 62 months, recurrent or metachronous neoplasia was detected in five patients, but repeat endoscopic treatment was successful in all of these patients. The calculated 5-year over all survival rate was 66%. However, no tumor-related death occurred in this series.

Those promising results suggest that endoscopic resection could be also successful in low-risk submucosal Barrett's cancer in a highly experienced center, but further data have to be awaited to draw final conclusions.

Ablative treatment methods for early Barrett's neoplasia

All ablative treatment methods have in common that they don't provide a specimen of the neoplastic lesion for exact histological confirmation of the infiltration depth and probable presence of infiltration of lymph vessels (L-status) or blood vessels (V-status). When treating neoplasia with one of the available ablative treatment modalities, a possible problem might be the underestimation of a neoplastic lesion and the endoscopist might end up treating a submucosal carcinoma or cancer infiltrating lymph vessels harboring lymphatic spread. Therefore, all visible and detectable lesions within the Barrett's segment should be treated by endoscopic resection.

Photodynamic therapy

Photodynamic therapy (PDT) has been successfully used to treat early neoplasia in Barrett's esophagus for more than one decade [23•,24,25]. Despite initial promising results, European centers changed from PDT to endoscopic resection several years ago [24,26]. In the USA, PDT has been regarded as the endoscopic treatment of choice until recently. In a large multicentric randomized trial utilizing intravenous porfimer sodium, a photosensitizer, 255 patients with HGIN were treated by PDT and proton pump inhibitors (PPIs) or PPI only. Complete ablation was possible in 77% of patients in the PDT arm compared with 39% of patients in the PPI arm. Significantly fewer patients progressed to cancer in the PDT arm than in the PPI arm (13 vs. 28%) [27]. However, complications occurred in 94% of the PDT group. Results were similar after 5 years of follow-up [28].

A major concern of PDT in patients with HGIN and cancer is the squamous overgrowth of neoplastic lesions after treatment. A very recent prospective randomized study [29•] was able to show that there was no significant difference in squamous overgrowth between patients treated by PDT or receiving omeprazole only, and more importantly, the highest grade of neoplasia was not found exclusively beneath squamous mucosa in any patient.

It has been shown that biomarkers seem to be able to predict the response of HGIN in Barrett's esophagus to PDT. Prasad *et al.* [30] demonstrated in 126 patients that p16 allelic loss predicted decreased response to PDT with an odds ration of 0.32. Other independent predictors of loss of dysplasia were the length of the Barrett's segment and the performance of PDT.

However, PDT has several disadvantages leading to a dramatic decrease of use of this method. PDT with porfimer sodium is expensive and associated with a high complication rate. Photosensitivity and stricture formation in up to 30% of patients are important drawbacks of this method. Recent studies were able to identify the following risk factors for stricture formation: multiple PDT courses [31,32], longer length of Barrett's esophagus [31], presence of intramucosal carcinoma [31], endoscopic resection before PDT [32], and prior history of esophageal stricture [32]. The use of 5-aminolevulinic acid as a photosensitizer for PDT was associated with considerably fewer complications and showed very good short and long-term results [24,26].

Radiofrequency ablation

In recent years, PDT has been replaced by radiofrequency ablation (RFA) of Barrett's epithelium in most centers. RFA utilizes a 3-cm balloon with circular electrodes delivering the energy designed for circumferential ablation (HALO-360). A focal device (HALO-90) fits over the tip of the endoscope and can be used for ablation of smaller areas [33]. In a US multicenter registry with 16 centers, the safety and efficacy of RFA in patients with HGIN in Barrett's esophagus were investigated [34•]. One hundred forty-two patients were treated by circumferential RFA with the HALO system. The median Barrett length was 6 cm. An endoscopic resection prior to ablative treatment was permitted in this study. Strictures occurred in only one patient and no buried glands were found during follow-up. Out of the 92 patients with at least one follow-up endoscopy, a complete removal of HGIN was confirmed in 90.2% and of Barrett's epithelium in 54.3%.

A large prospective randomized sham-controlled trial [35•] investigated the efficacy of RFA in 127 patients with LGIN ($n=63$) and HGIN ($n=64$) from 19 US centers. Patients were randomized (2 : 1) to RFA or sham treatment. The 1-year interim analysis was able to show that 74% of patients randomized to RFA achieved complete clearance of Barrett's metaplasia compared with 0% in the sham arm. RFA successfully removed HGIN in 83% of patients (10 out of 12 patients) and LGIN in 100% (23 out of 23 patients). In the sham group, 0% of patients had clearance of HGIN and 36% of LGIN. RFA was also able to reduce the rate of neoplasia progression from LGIN to HGIN or HGIN to cancer.

Two recently published studies [36,37] from the Amsterdam group combined endoscopic resection of visible neoplastic lesions with circumferential and focal RFA of the remaining Barrett's esophagus containing HGIN in 23 patients. Ablation without prior endoscopic resection was performed in 10 patients with flat HGIN. Complete elimination of neoplasia and Barrett's metaplasia was possible in all of the 23 included patients, and none of the 836 biopsies of the neosquamous mucosa contained subsquamous Barrett's esophagus.

RFA seems to provide a high rate of complete Barrett's eradication without residual Barrett's mucosa underneath the newly developed squamous epithelium ('buried glands'). In addition, the complication rate seems to be very low, especially compared with PDT. RFA seems to be the ideal addendum to endoscopic resection for ablation of the remaining nondysplastic Barrett's epithelium after successful resection of all localizable HGIN and adenocarcinoma. A removal of all neoplastic lesions by endoscopic resection provides a specimen that can be evaluated by the pathologist regarding infiltration depth and risk factors for lymphatic spread to prevent undertreatment. Afterwards, ablation of the nondysplastic Barrett's mucosa can significantly reduce the rate of metachronous neoplasia or recurrences [21•].

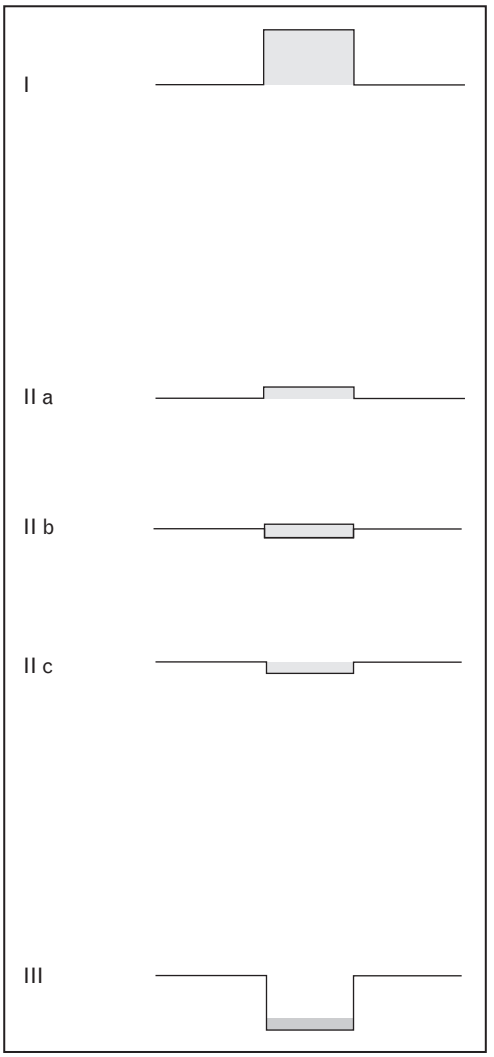
Endoscopic resection

Endoscopic resection of early neoplastic lesions has become increasingly important in recent years, both as a diagnostic tool for the staging of esophageal carcinomas and as a method of carrying out definitive treatment when the cancer meets certain criteria in which the risk of lymph node metastasis is negligible. Methods of endoscopic resection are snare resection with prior submucosal injection, the widely used 'suck and cut' technique, either with a cap or a ligation device, and endoscopic submucosal dissection (ESD).

Until recently, only few studies with larger patient numbers and longer follow-up were available for endoscopic resection. A recent study [20] has now provided excellent long-term results for endoscopic resection in 100 consecutive patients with low-risk mucosal Barrett's cancer. Low-risk Barrett's carcinoma was defined as a tumor limited to the mucosal layer, less than 20 mm in diameter, macroscopic type I, II, or both (Fig. 1), well and moderately differentiated, and no lymph or blood vessel infiltration. Complete remission could be achieved in 99% of patients, and the calculated 5-year overall survival rate was 98%. None of the patients died of Barrett's neoplasia in the study, and metachronous lesions were observed in only 11% after a mean of 36.7 months.

This study of endoscopic resection in a highly selected cohort of patients with low-risk Barrett's carcinoma does not reflect the general population of patients with

Figure 1 Macroscopic classification of superficial neoplastic lesions



Polypoid tumor (type I), flat and slightly elevated (IIa), flat and level (IIb), flat depressed (IIc), and ulcerated (III).

Barrett's neoplasia, but clearly underlines the safety and efficacy of the method in an expert center. The results with regard to the complete response rate and recurrence rate are slightly poorer in a general patient population with HGIN and mucosal Barrett's cancer with the majority not fulfilling low-risk criteria. However, the success rates are also excellent in these patients, as underlined by the largest series so far published for endoscopic treatment of Barrett's neoplasia, 349 patients with HGIN ($n = 61$) and with mucosal carcinoma ($n = 288$) were included. Endoscopic resection was performed in 279 patients, PDT with 5-aminolevulinic acid as a photosensitizer in 55 patients and both methods were combined in 13 patients for treatment of neoplastic Barrett's esophagus. Treatment was highly effective with a remission rate of 96.6%. However, during a median follow-up of more than 5 years, metachronous and recurrent neoplasia was observed in 21.5% of patients. Most patients were retreated successfully and long-term complete response was achieved in 94.5%. The overall 5-year survival rate in all patients was calculated as 84% and did not significantly differ from the survival of the average German population with the same age and sex distribution. Ablative treatment of the remaining nondysplastic Barrett's epithelium with argon–plasma coagulation or PDT was able to significantly reduce the rate of metachronous HGIN or cancer from 30 to 16.5% [21•].

An attractive concept to remove the whole Barrett's esophagus is stepwise radical endoscopic resection. The Amsterdam group [38] treated 37 patients with this concept. Complete eradication of early neoplasia was achieved in all 37 patients treated in a median number of three sessions, and complete removal of all Barrett's mucosa was achieved in 33 patients (89%). Symptomatic stenoses occurred in 26% of patients; further complications observed were one perforation and one case of delayed bleeding, all managed endoscopically. No recurrences had been observed after 11 months. The same authors recently reported on another group of 34 patients, HGIN and early cancer was removed by radical endoscopic resection in all patients and Barrett's esophagus was completely eradicated in 68% (23/34) of patients with the help of additional argon–plasma coagulation in 12 patients. HGIN and cancer recurred in 9% of patients. Perforation occurred in 6% of patients and 56% developed dysphagia because of stricture formation [39].

In conclusion, circumferential endoscopic resection of the whole Barrett's segment appears to be an interesting approach in order to prevent recurrences or metachronous lesions after successful eradication of malignancy. Major problems include the high stricture rate of more than 50% and the fact that despite this radical treatment, there is relevant residual Barrett's epithelium, with a recurrence rate of up to 11%. In addition, the follow-up periods and patient numbers were too limited in these studies for final conclusions to be drawn.

There is almost no experience with ESD in patients with early Barrett's neoplasia, especially in the Western world. In a smaller series published by Kakushima *et al.* [40], ESD was performed in 30 patients with tumors of the esophagogastric junction. Only four of the patients had early Barrett's cancer. The R0 resection rate was 97% (29 of 30). In a further publication, 24 patients with adenocarcinoma at the esophagogastric junction were treated by ESD [41]. The 'en-bloc' resection rate was 100% in this series but only 72% of lesions were judged as a curative resection. The lack of experience with ESD in Western counties, the demanding procedure itself, and long operation time in combination with the excellent results with conventional endoscopic resection make it very unlikely that ESD will play a major role in early Barrett's neoplasia in the near future.

Danger of ablative treatment in high-grade intraepithelial neoplasia and mucosal adenocarcinoma

From our point of view, sole ablation of localizable HGIN lesions or mucosal cancer harbors the risk of an undertreatment of undetected submucosal cancer that can be found in 12.7% of patients with HGIN who underwent esophagectomy [42•]. This risk seems to be even higher when ablation of HGIN is performed in less experienced centers. This hypothesis is underlined by the fact that about most HGIN and cancers are found in flat mucosa. In a large series with 380 HGIN and T1 adenocarcinomas, 78% (297/380) of all lesions were flat (macroscopic type II) (Fig. 1) and 12.5% of these lesions showed submucosal invasion [43].

These figures illustrate that ablation of flat HGIN or cancer may result in an undertreatment of about 10% of patients in whom esophagectomy would have been required. As 'only' 20–30% of those submucosal Barrett's cancer is associated with lymph node metastasis, large patient numbers and long follow-up are needed to demonstrate these fatal outcomes within studies.

Conclusion

Endoscopic treatment of early neoplasia in Barrett's esophagus (HGIN and mucosal adenocarcinoma) has become the method of choice in most countries. Long-term results for endoscopic treatment in a large group of patients are now available and are proving that endoscopic resection and PDT are well tolerated and highly effective with long-term complete remission rates of more than 94% [21•]. All visible lesions should be treated by endoscopic resection for histological confirmation of the neoplastic lesion. After successful endoscopic resection of all visible and localizable HGIN and mucosal

cancer, ablative treatment of the remaining Barrett's epithelium at risk should be performed in order to reduce the rate of recurrent or metachronous neoplasia. RFA seems to be the method for ablation with the highest rates of Barrett's eradication with a very low complication rate and an almost absent risk of residual 'buried glands' [34•,35•,36,37].

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

1 Pohl H, Welch HG. The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence. J Natl Cancer Inst 2005; 97:142–146.

2 Reid BJ, Levine DS, Longton G, *et al.* Predictors of progression to cancer in Barrett's esophagus: baseline histology and flow cytometry identify low- and high-risk patient subsets. Am J Gastroenterol 2000; 95:1669–1676.

3 Buttar NS, Wang KK, Sebo TJ, *et al.* Extent of high-grade dysplasia in Barrett's esophagus correlates with risk of adenocarcinoma. Gastroenterology 2001; 120:1630–1639.

4 Fountoulakis A, Zafirellis KD, Dolan K, *et al.* Effect of surveillance of Barrett's oesophagus on the clinical outcome of oesophageal cancer. Br J Surg 2004; 91:997–1003.

5 Aldulaimi DM, Cox M, Nwokolo CU, Loft DE. Barrett's surveillance is worthwhile and detects curable cancers. A prospective cohort study addressing cancer incidence, treatment outcome and survival. Eur J Gastroenterol Hepatol 2005; 17:943–950.

6 Pech O, May A, Rabenstein T, Ell C. Endoscopic resection of early oesophageal cancer. Gut 2007; 56:1625–1634.

7 O'Connor JB, Falk GW, Richter JE. The incidence of adenocarcinoma and dysplasia in Barrett's esophagus: report on the Cleveland Clinic Barrett's Esophagus Registry. Am J Gastroenterol 1999; 94:2037–2042.

8 Drewitz DJ, Sampliner RE, Garewal HS. The incidence of adenocarcinoma in Barrett's esophagus: a prospective study of 170 patients followed 4.8 years. Am J Gastroenterol 1997; 92:212–215.

9 Shaheen NJ, Crosby MA, Bozymski EM, Sandler RS. Is there publication bias in the reporting of cancer risk in Barrett's esophagus? Gastroenterology 2000; 119:333–338.

10 Wang KK, Sampliner RE, Practice Parameters Committee of the American College of Gastroenterology. Updated guidelines 2008 for the diagnosis, surveillance and therapy of Barrett's esophagus. Am J Gastroenterol 2008; 103:788–797.

11 Koop H, Schepp W, Muller-Lissner S, *et al.* Consensus conference of the DGVS on gastroesophageal reflux. Z Gastroenterol 2005; 43:163–164.

12 Standards of Practice Committee of the American Society for Gastrointestinal Endoscopy. ASGE guideline: the role of endoscopy in the surveillance of premalignant conditions of the upper GI tract. Gastrointest Endosc 2006; 63:570–580.

13 Playford RJ. New British Society of Gastroenterology (BSG) guidelines for the diagnosis and management of Barrett's oesophagus. Gut 2006; 55:442.

14 Wani S, Puli SR, Shaheen NJ, *et al.* Esophageal adenocarcinoma in Barrett's esophagus after endoscopic ablative therapy: a meta-analysis and systematic review. Am J Gastroenterol 2009; 104:502–513.

15 Schnell TG, Sontag SJ, Chejfec G, *et al.* Long-term nonsurgical management of Barrett's esophagus with high-grade dysplasia. Gastroenterology 2001; 120:1607–1609.

16 Pech O, Vieth M, Schmitz D, *et al.* Conclusions from the histological diagnosis of low grade intraepithelial neoplasia in Barrett's oesophagus. Scand J Gastroenterol 2007; 42:682–688.

17 Reid BJ, Prevo LJ, Galipeau PC, *et al.* Predictors of progression in Barrett's esophagus II: baseline 17p (p53) loss of heterozygosity identifies a patient subset at increased risk for neoplastic progression. Am J Gastroenterol 2001; 96:2839–2848.

18 Buskens CJ, Westerterp M, Lagarde SM, *et al.* Prediction of appropriateness of local endoscopic treatment for high-grade dysplasia and early adenocarcinoma by EUS and histopathologic features. Gastrointest Endosc 2004; 60:703–710.

19 Stein HJ, Feith M, Bruecher BLDM, *et al.* Early esophageal squamous cell and adenocarcinoma: pattern of lymphatic spread and prognostic factors for long term survival after surgical resection. Ann Surg 2005; 242:566–573.

20 Ell C, May A, Pech O, *et al.* Curative endoscopic resection of early esophageal adenocarcinomas (Barrett's cancer). Gastrointest Endosc 2007; 65:3–10.

21 • Pech O, Behrens A, May A, *et al.* Long-term results and risk factor analysis for recurrence after curative endoscopic therapy in 349 patients with high-grade intraepithelial neoplasia and mucosal adenocarcinoma in Barrett's oesophagus. Gut 2008; 57:1200–1206.

This is the first publication providing long-term results for the endoscopic treatment of patients with HGIN and mucosal Barrett's carcinoma in a large group of patients. Results also suggest that ablative treatment of the remaining nondysplastic Barrett's epithelium can significantly reduce the rate of recurrent neoplasia.

22 Barr H, Shepherd NA, Dix A, *et al.* Eradication of high-grade dysplasia in columnar-lined (Barrett's) oesophagus by photodynamic therapy with endogenously generated protoporphyrin IX. Lancet 1996; 348:584–585.

23 • Manner H, May A, Pech O, *et al.* Early Barrett's carcinoma with 'low-risk' submucosal invasion: long-term results of endoscopic resection with a curative intent. Am J Gastroenterol 2008; 103:2589–2597.

The results of this study suggest that endoscopic resection seems to be well tolerated also in patients with incipient infiltration of the submucosal layer (pT1sm1) without further risk factors.

24 Gossner L, Stolte M, Sroka R, *et al.* Photodynamic ablation of high-grade dysplasia and early cancer in Barrett's esophagus by means of 5-aminolevulinic acid. Gastroenterology 1998; 114:448–455.

25 Overholt BF, Panjehpour M, Haydek JM. Photodynamic therapy for Barrett's esophagus: follow-up in 100 patients. Gastrointest Endosc 1999; 49:1–7.

26 Pech O, Gossner L, May A, *et al.* Long-term results of photodynamic therapy with 5-aminolevulinic acid for superficial Barrett's cancer and high-grade intraepithelial neoplasia. Gastrointest Endosc 2005; 62:24–30.

27 Overholt BF, Lightdale CJ, Wang KK, *et al.* Photodynamic therapy with porfimer sodium for ablation of high-grade dysplasia in Barrett's esophagus: international, partially blinded, randomized phase III trial. Gastrointest Endosc 2005; 62:488–498.

28 Overholt BF, Wang KK, Burdick JS, *et al.* Five-year efficacy and safety of photodynamic therapy with photofrin in Barrett's high-grade dysplasia. Gastrointest Endosc 2007; 66:460–468.

29 • Bronner MP, Overholt BF, Taylor SL, *et al.* Squamous overgrowth is not a safety concern for photodynamic therapy for Barrett's esophagus with high-grade dysplasia. Gastroenterology 2009; 136:56–64.

This large multicenter trial was able to demonstrate that squamous reepithelialization after PDT was not a safety concern. The highest degree of neoplasia was never found underneath neosquamous epithelium only.

30 Prasad GA, Wang KK, Halling KC, *et al.* Utility of biomarkers in prediction of response to ablative therapy in Barrett's esophagus. Gastroenterology 2008; 135:370–379.

31 Yachimski P, Puricelli WP, Nishioka NS. Patient predictors of esophageal stricture development after photodynamic therapy. Clin Gastroenterol Hepatol 2008; 6:302–308.

32 Prasad GA, Wang KK, Buttar NS, *et al.* Predictors of stricture formation after photodynamic therapy for high-grade dysplasia in Barrett's esophagus. Gastrointest Endosc 2007; 65:60–66.

33 Sharma VK, Wang KK, Overholt BF, *et al.* Balloon-based, circumferential, endoscopic radiofrequency ablation of Barrett's esophagus: 1-year follow-up of 100 patients. Gastrointest Endosc 2007; 65:185–195.

34 • Ganz RA, Overholt BF, Sharma VK, *et al.* Circumferential ablation of Barrett's esophagus that contains high-grade dysplasia: a U.S. Multicenter Registry. Gastrointest Endosc 2008; 68:35–40.

This study demonstrated that RFA of patients with HGIN seems to be well tolerated and effective in multiple US centers. HGIN could be eradicated in 90% of patients.

35 • Shaheen NJ, Sharma P, Overholt RF, *et al.* A randomized, multicenter, sham-controlled trial of radiofrequency ablation for subjects with Barrett's esophagus containing dysplasia. N Engl J Med (in press).

This trial was able to show in a prospective sham-controlled trial that RFA is significantly more effective than sham treatment. However, in only 10 out of 15 patients, HGIN could be successfully eradicated.

36 Gondrie JJ, Pouw RE, Sondermeijer C, *et al.* Effective treatment of early Barrett's neoplasia with stepwise circumferential and focal ablation using the HALO system. Endoscopy 2008; 40:370–379.

37 Gondrie JJ, Pouw RE, Sondermeijer C, *et al.* Stepwise circumferential and focal ablation of Barrett's esophagus with high-grade dysplasia: results of the first prospective series in 11 patients. Endoscopy 2008; 40:359–369.

38 Peters FP, Kara MA, Rosmolen WD, *et al.* Stepwise radical endoscopic resection is effective for complete removal of Barrett's esophagus with early neoplasia: a prospective study. Am J Gastroenterol 2006; 101:1449–1457.

39 Pouw RE, Peters FP, Sempoux C, *et al.* Stepwise radical endoscopic resection for Barrett's esophagus with early neoplasia: report on a Brussels' cohort. Endoscopy 2008; 40:892–898.

40 Kakushima N, Yahagi N, Fujishiro M, *et al.* Efficacy and safety of endoscopic submucosal dissection for tumors of the esophagogastric junction. Endoscopy 2006; 38:170–174.

41 Yoshinaga S, Gotoda T, Kusano C, *et al.* Clinical impact of endoscopic submucosal dissection for superficial adenocarcinoma located at the esophagogastric junction. Gastrointest Endosc 2008; 67:202–209.

42 Konda VJ, Ross AS, Ferguson MK, *et al.* Is the risk of concomitant invasive • esophageal cancer in high-grade dysplasia in Barrett's esophagus overestimated? Clin Gastroenterol Hepatol 2008; 6:159–164.
This study demonstrates that 12.7% of patients with HGIN undergoing esophagectomy have submucosal Barrett's cancer. Those data nicely show that endoscopic resection of all localizable neoplastic lesions in Barrett's esophagus should be treated by endoscopic resection in order to obtain a specimen for histological work up. Ablative treatment would be an undertreatment in more than 10% of patients with HGIN.

43 Pech O, Gossner L, Manner H, *et al.* Prospective evaluation of the macroscopic types and location of early Barrett's neoplasia in 380 lesions. Endoscopy 2007; 39:588–593.