

Do the guidelines for management of dysplasia in Barrett's esophagus reflect current best practice?



Angelika Behrens*¹ & Oliver Pech¹

Practice Points

- Endoscopic resection of dysplasia and early carcinoma in Barrett's esophagus must not be regarded as equivalent to esophageal resection, as the surgical procedure is associated with substantial rates of mortality and morbidity.
- Endoscopic resection is the treatment of choice for dysplasia and early esophageal adenocarcinoma.
- Histological examination of the resected specimen can identify risk factors for nodal metastasis – for example, sm1 infiltration – so that a secondary treatment recommendation for esophageal resection is possible in individual cases.
- Thermoablative procedures are essential in the treatment of non-neoplastic Barrett's esophagus; they have no value in the treatment of early neoplastic changes.

SUMMARY Guidelines are essential reference points in everyday clinical work. They are intended to provide physicians with essential information for diagnostic and therapeutic decision-making. With regard to the treatment recommendations issued by the various specialist societies on the treatment of dysplasia and early mucosal carcinoma in Barrett's esophagus, the range of recommendations given (from exclusively local thermal therapy to esophageal resection, recommended as equivalent) is, for the present authors, difficult to understand against the background of the current literature. In the presence of dysplasia or early mucosal carcinoma, endoscopic resection is, in our view, absolutely necessary. Obtaining a histological sample is the central pillar of every type of oncological treatment and should also be regarded as the mandatory standard for neoplasia in Barrett's esophagus.

¹Medizinische Klinik II, HSK Dr Horst Schmidt Kliniken GmbH (Teaching Hospital of the University of Mainz), Ludwig-Erhardt-Strasse 100, 65199 Wiesbaden, Germany
*Author for correspondence: Tel.: +49 611 43 2420; Fax: +49 611 43 9820; angelika.behrens@hsk-wiesbaden.de

The guidelines and position papers published by the various specialist societies are an essential tool for quality assurance in medicine, allowing the latest research results to find their way into routine clinical practice. However, the extremely elaborate process of preparing guidelines often leads to a substantial time delay before the publication and reception of new scientific findings. In addition, guidelines are strongly influenced by experiences in different countries and regionally available treatment options, as well as the political interests of the various professional associations. They nevertheless provide an essential reference point for practical medical work.

There are few areas of gastrointestinal endoscopy in which such substantial new insights, which fundamentally alter therapy, have been seen in recent years as the treatment of dysplasia and mucosal carcinomas in Barrett's esophagus. This article investigates the extent to which these new insights have been included or discussed in the various national and international guidelines.

Intramucosal adenocarcinoma in Barrett's esophagus

When a diagnosis of mucosal adenocarcinoma in Barrett's esophagus has been established, the treatment recommendation, published in 2011 by the American Gastroenterological Association (AGA), is to carry out esophageal resection [1]. By contrast, the guidelines published by the Society of American Gastrointestinal Endoscopic Surgeons (SAGES) in 2010 recommend carrying out local endoscopic therapy in the form of endoscopic resection, radiofrequency ablation (RFA), photodynamic therapy (PDT) or a combination of these procedures. According to the guidelines, surgical therapy should be carried out when endoscopic treatment administered with curative intent has failed. Esophageal resection may also be recommended as a primary treatment procedure, according to SAGES [2]. Identical recommendations are given in a statement on Barrett's esophagus issued by NICE in 2010, which advises esophageal resection or endoscopic resection, with or without ablation of the Barrett's mucosa [101]. In the American College of Gastroenterology (ACG)'s updated guidelines on the diagnosis, surveillance and therapy of Barrett's esophagus, published in 2008, no position is taken on the treatment of intramucosal Barrett's adenocarcinoma [3].

The various guidelines thus contain a wide range of treatment recommendations in patients

diagnosed with intramucosal Barrett's adenocarcinoma; both low-risk procedures with endoscopic therapy and also esophageal resection are in accordance with the guidelines. This is in spite of the fact that studies published in respected journals have shown that esophageal resection and endoscopic resection of early tumors in the esophagus are not in fact equivalent treatment procedures.

Although no prospective and randomized studies have been published comparing esophageal resection with endoscopic therapy for intramucosal adenocarcinoma in Barrett's esophagus, the data are nevertheless clear and consistent with regard to the large differences in the mortality and morbidity rates associated with esophageal resection in comparison with endoscopic therapy [4,5]. In the literature, esophageal resection procedures are associated with a morbidity rate of 30–50% and a mortality rate of 2–3% [6–8]. In various studies in which endoscopic therapy was administered for mucosal Barrett's adenocarcinoma, the mortality rate was 0% and the morbidity rate was in the range of 0–13% [9–11].

A retrospective cohort study by Prasad *et al.* included 178 patients who received either esophageal resection or endoscopic resection. In this group, the mortality rate in the surgical group was 4%, with a morbidity rate of 34%, while none of the patients who received endoscopic treatment died and the morbidity rate in that group was reported as 13%. No significant differences in the overall survival were observed [4]. Very similar results were reported in a two-center retrospective cohort study published in 2011, reporting a mortality rate in the surgical group of 2.6% in comparison with 0% in endoscopically treated patients, with morbidity rates of 32 versus 0% [5]. With almost identical results, these two studies show that esophageal resection is associated with much higher mortality and morbidity rates in comparison with local endoscopic therapy. In addition, validated long-term data for more than 1000 patients are available on the oncological safety of local endoscopic therapy in patients with a diagnosis of intramucosal adenocarcinoma [9–11].

In view of these data, an equivalent recommendation of both treatment options – endoscopic therapy or esophageal resection – is difficult to understand, and for a patient undergoing esophageal resection it implies a substantial risk of permanent impairment of health, in addition to the

existing risk of mortality. A recommendation of endoscopic therapy presupposes, of course, that the patient is being treated at an interventional center with expertise in endoscopy and that regular expert endoscopic follow-up examinations are carried out.

In addition, when one examines the SAGES recommendations in detail, endoscopic therapy in accordance with the guidelines may consist of RFA, PDT, endoscopic resection or a combination of these treatment procedures. In our opinion, there is no justification on the basis of the available data for recommending thermal therapy alone for early neoplasia in Barrett's esophagus. Two major studies in this context are those by Moss *et al.* and Konda *et al.* When there was biopsy evidence of high-grade intraepithelial neoplasia (HGIN), histological evidence of submucosal carcinoma was already present in 11% of cases [12,13]. When thermal therapy is administered, there is therefore a substantial risk of lymph node metastasis for the individual patient. This risk does not arise if primary endoscopic resection is carried out, since risk stratification can be carried out using the histological resection specimen. For example, if the resection specimen shows submucosal infiltration by the tumor, esophageal resection can be recommended for the patient. It cannot be repeated often enough that the macroscopic appearance or biopsy-based histological diagnosis is not sufficiently predictive to serve as a substitute for staging by histological assessment.

High-grade intraepithelial neoplasia

Against the background of these data, what recommendations are given in the various guidelines when HGIN in Barrett's esophagus is diagnosed? The AGA's treatment recommendations for patients with a diagnosis of HGIN range from esophageal resection, to the option of endoscopic resection for visible neoplastic changes, thermal therapy for shallow lesions or HGIN that cannot be visually located, to inclusion of the patient in a 3-month endoscopic surveillance program. The ACG gives similar recommendations. The NICE recommendations are almost identical, the sole difference being that exclusive endoscopic surveillance is not included in the position paper. The SAGES treatment guidelines do not differentiate between a diagnosis of HGIN and mucosal adenocarcinoma, so that endoscopic resection and thermal endoscopic procedures

are mentioned as treatment options alongside esophageal resection.

We cannot agree with the guidelines that, when there is histological evidence of HGIN in Barrett's esophagus without an endoscopically visible lesion, thermal therapy (e.g., radiofrequency therapy) or esophageal resection should be a recommended approach in addition to endoscopic monitoring. If a histological diagnosis of HGIN is confirmed by an experienced gastrointestinal pathologist and the neoplastic lesion is not detectable, close endoscopic monitoring should be carried out to allow the lesion to be located during the subsequent course. Alternatively, stepwise endoscopic resection of the Barrett's mucosa can be performed by Pouw *et al.* [11]. Choosing this method, one has to bear in mind a stenosis rate of up to 50%. By whatever means – a close follow-up or extensive endoscopic resection – a resection technique is the only way to obtain a resection specimen and achieve a conclusive histological diagnosis. It allows histological processing with assessment of the stage of neoplasia and, in the case of carcinoma, of the depth of invasion (pT1m1–4; pT1sm1–3), along with details of possible lymphatic spread (L status) or venous infiltration (V status). The pathologist can provide information on whether the area of the resection margins is free of neoplasia laterally and – much more importantly – at the base (R0, R1). Numerous studies have shown that the histological diagnosis made at the time of endoscopic resection is revised in comparison with the preinterventional biopsy in up to 50% of cases [14]. These are all fundamental considerations, on the basis of which endoscopic resection must always be preferable to thermoablative procedures.

The Amsterdam group performed RFA in Barrett's esophagus with HGIN without visible abnormalities; however, this study has limitations [10,15]: first, the study included as few as 26 patients; second, the mean follow-up was too short at 29 months from an oncological perspective; and third, complete remission was achieved only in 83%, compared with our data, which reported above 96%.

In our view, thermoablative procedures, including RFA, undoubtedly have a place in endoscopic therapy for Barrett's esophagus with evidence of neoplasia. However, we believe that it should be exclusively used as an additional method after endoscopic resection of neoplasia, to ablate the

remaining non-neoplastic Barrett's esophagus. In a prospective and randomized study by our own research group, which was presented at the 2010 Digestive Disease Week, it was shown that ablation of non-neoplastic Barrett's mucosa after endoscopic resection reduces the rate of recurrences and metachronous carcinomas by 30% in comparison with monitoring alone [16].

Although multicenter prospective randomized studies and even sham-controlled studies are available for PDT, PDT can now be regarded as obsolete, due to the high complication rate associated with the method [17]. In contrast to the AGA position paper, we can no longer recommend this form of treatment in view of its poor results, the alternatives that are now available and the disadvantages of ablative therapy already referred to above.

Cryotherapy is a new interesting therapeutic tool for Barrett's ablation. From our perspective, it is not recommended for therapy of neoplastic lesions in Barrett's esophagus because of the reasons mentioned above. Prospective, randomized studies comparing cryotherapy with, for example, RFA are not available. In fact, there is no evidence for using cryotherapy for Barrett's ablation beyond studies.

Low-grade intraepithelial neoplasia

What treatment regimens do the individual societies regard as indicated when low-grade intraepithelial neoplasia (LGIN) is diagnosed? The AGA envisages endoscopic monitoring alone every 6–12 months if LGIN is diagnosed. The ACG recommends endoscopic resection if visible changes are present, or monitoring as well if the Barrett's esophagus is macroscopically unremarkable. The SAGES and NICE papers do not include any statements by the societies regarding what procedure to follow when LGIN is diagnosed.

Studies have shown that histological classification of LGIN is difficult, particularly when there is simultaneous inflammation in the area biopsied. In a study by Curvers *et al.*, only 15% of the changes initially classified as LGIN were actually confirmed as LGIN by pathologists specializing in gastroenterology; the diagnosis was downgraded in 85% of the cases. When patients with confirmed LGIN are followed up endoscopically, progression from LGIN to HGIN or mucosal carcinoma is found to occur in 42% of cases during a 4-year follow-up period [18]. On the basis of these data, two points are important:

- Diagnosis of LGIN should always be confirmed by pathologists specializing in gastroenterology;
- Endoscopic resection, in our view, is indicated when there is a confirmed diagnosis of LGIN and a visible lesion. If the lesion is not visible, a close endoscopic follow-up is recommended. Alternatively, thermoablative therapy, for example with RFA, should be performed in a study setting.

The multicenter SURF study by Bergman's group, which is currently recruiting patients and is using a randomized and prospective design to compare the surveillance strategy with thermoablative RFA procedures, will be able to provide new findings on this issue in the future [102].

Conclusion

In summary, we regard the poorly differentiated treatment strategies that are recommended by the above-mentioned specialist societies as difficult to understand against the background of data currently available. In the presence of dysplasia or early mucosal carcinoma, endoscopic resection is, in our view, absolutely necessary. Obtaining a histological sample is the central pillar of every type of oncological treatment and should also be regarded as the mandatory standard for neoplasia in Barrett's esophagus. Additional thermal ablation of non-neoplastic Barrett's mucosa can significantly reduce the risk of recurrence and lead to excellent long-term results.

Guidelines are essential reference points in everyday clinical work. They are intended to provide physicians with essential information for diagnostic and therapeutic decision-making. With regard to the treatment recommendations issued by the various specialist societies on the treatment of dysplasia and early mucosal carcinoma in Barrett's esophagus, the range of recommendations given – from exclusively local thermal therapy to esophageal resection, recommended as equivalent – is, for the present authors, difficult to understand against the background of the current literature. In our view, the central recommendation in the treatment of dysplasia and mucosal adenocarcinoma in Barrett's esophagus can only be as follows: endoscopic resection of all neoplastic lesions is crucial for risk stratification. Endoscopic resection must be the treatment of choice for early neoplasia in the esophagus. In contrast to thermoablative procedures, it allows comprehensive diagnostic accuracy and also, in most cases,

represents definitive treatment. It is also a safe and organ-preserving therapeutic procedure. When the treatment is combined with local ablative thermal therapy, the risk of recurrence is low and the long-term prognosis is excellent.

Future perspective

In the future, it would be ideal if patients could be differentiated – for example, using a genetic profile – into one group with and one without a risk of malignant changes, with the corresponding surveillance strategies then being developed. In addition, the development of a thermal ablation procedure to destroy non-neoplastic Barrett's mucosa following successful treatment for

dysplasia or early carcinoma would be desirable. This would allow safe and (in particular) complete ablation without leaving behind so-called 'buried glands'.

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