

## Tailored therapy for early Barrett's lesions

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Published online in Wiley InterScience (www.bjs.co.uk). DOI: 10.1002/bjs.5093

Under normal conditions the oesophagus is lined by non-keratinized squamous epithelium. Chronic reflux can induce metaplastic changes, whereby the squamous mucosa is replaced by columnar epithelium. The clinical significance of this so-called Barrett's oesophagus is related to its increased potential for malignant degeneration, especially when the columnar epithelium demonstrates specialized intestinal metaplasia (that is when goblet cells are present). Over the past few decades, the incidence of adenocarcinoma arising on a background of Barrett's change has increased markedly in the Western world. This rising incidence and the poor prognosis of symptomatic Barrett's cancer have led clinicians to recommend endoscopic surveillance of patients with intestinal metaplasia. Although the clinical value and cost-effectiveness of surveillance programmes are open to debate, they do tend to identify Barrett's lesions at earlier and more favourable stages<sup>1</sup>.

The process of malignant degeneration in a Barrett's segment is characterized by a stepwise progression from intestinal metaplasia, via low-grade dysplasia and high-grade dysplasia (HGD), into invasive adenocarcinoma, and mostly follows a multifocal and mosaic pattern<sup>2</sup>. Although the natural history of this process is still largely unknown, it offers an attractive window for early cancer detection. Because conventional endoscopy does not reliably discriminate between metaplastic and dysplastic tissue, a systematic programme of extensive random biopsies for histological evaluation is necessary,

although this strategy remains hampered by a potential for substantial sampling error.

Until recently it was generally accepted that the detection of HGD in an otherwise fit patient was an indication for 'prophylactic' oesophagectomy<sup>3</sup>. Owing to the limited accuracy of endoscopy, around 40 per cent of these patients already have an invasive cancer on careful histological examination of the resection specimen, whereas the remaining 60 per cent are known to have a high risk of developing cancer within months or a few years. Surgical resection was claimed to be safe with radical removal of all malignant and 'at-risk' Barrett's mucosa in combination with any lymph node metastases, thus offering excellent long-term outcomes<sup>4</sup>.

Recent advances in endoscopy may have changed the indications for surgical treatment in these patients. High-resolution endoscopes supplemented with staining techniques provide the endoscopist with enhanced images, targeting areas for biopsy. New imaging techniques (narrow band imaging and video-autofluorescence endoscopy) hold promise for even better endoscopic detection of dysplasia. In addition, endoscopic mucosal resection (EMR) allows safe removal of relatively large focal lesions in a Barrett's oesophagus, further optimizing diagnostic evaluation of these patients<sup>5</sup>. In consequence, the chances of missing an invasive cancer in a patient with HGD are much smaller than reported in the past, especially if diagnostic EMR is performed with a low threshold.

Apart from being an important diagnostic tool, EMR is also a therapeutic option in selected patients with early Barrett's cancer. Several small studies have suggested that EMR can successfully remove early neoplasia with a low rate of severe complications (less than 5 per cent)<sup>5,6</sup>, although EMR is associated with a recurrence rate of 25–30 per cent during the first 3 years when used in isolation for HGD or early cancer<sup>5</sup>. Although these recurrences can effectively be re-treated endoscopically<sup>5,6</sup>, this is considered an important drawback, necessitating strict endoscopic follow-up after endoscopic treatment. To prevent recurrence, some centres treat residual Barrett's mucosa after EMR with ablation therapy (mainly photodynamic therapy; PDT)<sup>6</sup>. In this scenario, EMR is performed initially to remove the dysplastic or neoplastic area within the Barrett's segment, allowing optimal histological evaluation and risk assessment of lymphatic dissemination. Provided that the EMR specimen shows no evidence of submucosal invasion, the remainder of the Barrett's epithelium is subsequently ablated using PDT. Lymphatic dissemination is known to be related to the depth of invasion and, provided that the neoplastic lesion is limited to the mucosa, the risk of positive nodes is only about 1 per cent. As soon as the tumour reaches the submucosa, however, this risk rapidly increases<sup>7</sup>. On this basis, mucosal lesions are potentially suitable for local endoscopic therapy, whereas lesions invading into the submucosa need surgical resection.

In the USA, ablation therapy with Photofrin® (Wyeth-Ayerst Lederle, Inc., Collegeville, PA, USA) PDT is becoming increasingly used as an alternative to surgery for patients with HGD<sup>8</sup>. PDT may, however, be associated with subsquamous Barrett's mucosa (sometimes referred to as 'buried glands') that can give rise to recurrent lesions during follow-up. In addition, PDT is associated with oesophageal stenosis in 30 per cent of patients and provides no histological material when used in isolation, potentially leading to undertreatment of patients who have lesions invading into the submucosa.

Sufficient evidence has now accumulated to support the endoscopic treatment of early Barrett's lesions as an alternative to surgery in selected patients. Optimal management of these patients requires referral to centres with appropriate technical expertise. Endoscopic investigations should include a 1-cm four-quadrant random biopsy protocol. This requires high-quality endoscopic equipment and expertise in the use of different imaging techniques for the optimal detection of subtle mucosal abnormalities. Reliable histological evaluation of biopsies and endoscopic resection specimens requires an experienced team of pathologists<sup>9</sup>.

EMR should now be considered the mainstay of therapy for mucosal lesions. Ablative techniques such as PDT should be regarded as an adjunct to endoscopic resection techniques. The most important problem currently lies with recurrence during follow-up. Strict endoscopic follow-up with a rigorous biopsy protocol is therefore imperative in order to detect and categorize recurrent lesions at

an early stage. Experimental endoscopic techniques permitting radical resection of the entire Barrett's segment are likely to become clinically available.

While mucosal lesions with only a very low risk of lymphatic dissemination have been shown to be suitable for endoscopic management, the role of surgery in patients with submucosal disease has continued to evolve. Transthoracic resection with extended lymphadenectomy, transhiatal resection with limited lymphadenectomy, vagus-sparing oesophagectomy and distal oesophageal resection with jejunal interposition all have their advocates. Limited surgery might be more logically applied as sentinel node techniques develop for oesophageal neoplasia, but the surgical community should equally remember that half of the patients with submucosal disease treated by transhiatal resection develop recurrent disease within 5 years, highlighting the fact that some patients may require extensive surgery and/or neoadjuvant therapies to improve survival<sup>7</sup>.

## References

- 1 van Sandick JW, van Lanschot JJB, Kuiken BW, Tytgat GNJ, Offerhaus GJA, Obertop H. Impact of endoscopic biopsy surveillance of Barrett's oesophagus on pathological stage and clinical outcome of Barrett's carcinoma. *Gut* 1998; **43**: 216–222.
- 2 van Sandick JW, van Lanschot JJB, ten Kate FJW, Offerhaus GJA, Fockens P, Tytgat GNJ *et al.* Pathology of early invasive adenocarcinoma of the esophagus or esophagogastric junction; implications for therapeutic decision making. *Cancer* 2000; **88**: 2429–2437.
- 3 Stein HJ. Esophageal cancer: screening and surveillance. Results of a consensus conference held at the VIth World Congress of the International Society for Diseases of the Esophagus. *Dis Esoph* 1996; **9**: S3–S19.
- 4 Heitmiller RF, Redmond M, Hamilton SR. Barrett's esophagus with high-grade dysplasia: an indication for prophylactic esophagectomy. *Ann Surg* 1996; **224**: 66–71.
- 5 May A, Gossner L, Pech O, Fritz A, Gunter E, Mayer G *et al.* Local endoscopic therapy for intraepithelial high-grade neoplasia and early adenocarcinoma in Barrett's oesophagus: acute-phase and intermediate results of a new treatment approach. *Eur J Gastroenterol Hepatol* 2002; **14**: 1085–1091.
- 6 Peters FP, Kara MA, Rosmolen WD, ten Kate FJ, Bultje AC, Krishnadath KK *et al.* Endoscopic resection combined with photodynamic therapy for high-grade dysplasia and early cancer in Barrett's esophagus. *Gastrointest Endosc* 2005; **61**: 506–514.
- 7 Westerterp M, Koppert LB, Buskens CJ, Tilanus HW, ten Kate FJW, Bergman JJGHM *et al.* Outcome of surgical treatment for early adenocarcinoma of the esophagus or gastro-esophageal junction. *Virchows Arch* (in press).
- 8 Overholt BF, Lightdale CJ, Wang K, Canto M, Burdick S, Barr H *et al.* International, multicenter, partially blinded, randomised study of the efficacy of photodynamic therapy (PDT) using porfimer sodium (POR) for ablation of high-grade dysplasia (HGD) in Barrett's esophagus (BE): results of 24-month follow-up. *Gastroenterology* 2003; **124**(Suppl 1): A20 (Abstract).
- 9 Kara MA, Bergman JJ, Tytgat GN. Follow-up for high-grade dysplasia in Barrett's esophagus. *Gastrointest Endosc Clin N Am* 2003; **13**: 513–533.