

LOCAL THERAPIES AND RESECTION IN BARRETT'S OESOPHAGUS AND EARLY OESOPHAGOGASTRIC CANCER

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Abstract

Endoscopic treatment to eliminate Barrett's Oesophagus, associated dysplasia and intramucosal cancer, in order to induce squamous re-epithelialisation has been developed as a viable, oesophagus-sparing alternative for eligible patients in recent years. It has gained popularity given its less invasive nature and better tolerability relative to radical oesophagectomy. Widely used modalities include endoscopic mucosal resection, radiofrequency ablation, argon plasma coagulation, photodynamic therapy and cryotherapy, each having their own advantages and limitations. Yet invasion of dysplasia into and beyond the submucosal layer of epithelium signifies potential metastasis, rendering endoscopic intervention no longer appropriate, and surgical intervention remains the definitive treatment. This review highlights the disease process of Barrett's Oesophagus and associated dysplasia and early cancer, the various treatment options and appropriate selection of patients, indications and management considerations.

The emergence of innovative endoscopic ablative therapies has shifted the treatment of Barrett's Oesophagus (BO) with dysplasia and early intramucosal cancer in selected patients from surgical to an endoscopic approach. This strategy is considered a genuine option after careful search for invasive cancer, in both surgically-fit and unfit patients. Yet oesophagectomy remains the definitive treatment modality, ensuring the highest cure rate for any associated oesophageal adenocarcinoma and ultimate risk reduction. Here we aim to outline the natural history and various therapeutic options, and to establish current recommendations in practice regarding the appropriate treatment selection.

BO is a condition characteristically of the Caucasian male, where normal squamous epithelium is replaced by columnar epithelium over any length in the distal oesophagus. It is thought to develop as a response to gastrooesophageal reflux disease through injury to the squamous epithelium.¹ Diagnosis is based on endoscopic appearance, as well as histological confirmation of specialised intestinal metaplasia, with mucin-producing goblet cells.

Latest data suggests an 8-20% prevalence rate of BO in Western countries among patients undergoing endoscopies for reflux symptoms.² This precancerous condition has potential to progress to oesophageal adenocarcinoma, one of the fastest rising malignancies, with its rate of increase being six to seven fold higher than most common cancers, including lung, breast, prostate, colorectal and melanoma.³ A progression through a series of cellular changes, from intestinal metaplasia through low grade dysplasia and high grade dysplasia (HGD) to oesophageal adenocarcinoma is postulated. The degree of dysplasia is thought to be strongly associated with the risk of carcinoma in patients with BO. The conversion rate of non-dysplastic BO into oesophageal adenocarcinoma

is 0.27- 0.5% per person-year,^{4,5} and that of HGD into oesophageal adenocarcinoma being much higher at 16-60% over up to eight years of follow up.⁶⁻⁸

Recent evidence suggests that patients with a columnar oesophagus but, without goblet cells on histology, may be especially at risk for transition to oesophageal adenocarcinoma, thereby querying the significance of goblet cells as a precondition in the neoplastic progression of BO.⁹

Epidemiological observations consistently associate BO with obese Caucasian males. A focus of recent investigation has been on genetic predisposition given that there is a familial risk of BO. In a sib-pair genome wide linkage study, three loci associated with the genes MSR1, ASCC1 and CTHRC1 were identified; further, mutations were found in each of these genes, with functional up-regulation of CCND1 which is downstream to MSR1. Further studies are anticipated.¹⁰

Current recommendations for practice

Intestinal Metaplasia

Currently, there is no Australian guideline regarding surveillance of patients with BO without dysplasia. The British Society of Gastroenterology recommends surveillance every two years,¹¹ while the American College of Gastroenterology recommends two endoscopies with biopsy within one year, and then follow-up with endoscopy every three years.¹² Although the changes seen in BO are a step towards the development of cancer, the overall progression rate to adenocarcinoma is low. Given this relatively low risk, and the restricted treatments currently available, more aggressive interventions such as ablation and resection are not advised in Australia for uncomplicated BO.

Dysplasia

Once dysplasia has been diagnosed, there is a significant risk of progression to cancer. The progression rate of HGD has been reported to be 16-60% spanning five to eight years of follow-up.⁶⁻⁸ Management for dysplasia is controversial and complex, especially that of HGD, with much debate surrounding the best intervention. Firstly, it is important to determine whether HGD is unifocal, multifocal, or associated with any visual mucosal abnormalities (VMA) such as nodularity, or ulceration. The presence of diffuse or multifocal HGD is associated with a higher risk (four-fold) of developing adenocarcinoma compared with focal HGD without VMA ($p=0.02$);¹³ any VMA may signify the presence of underlying cancer. In our experience in Melbourne, confocal endomicroscopy which enables 1000x magnification to 250 microns into the mucosa and submucosa, has proved useful in confirming high grade dysplasia, suspecting low grade dysplasia, and defining the margins of dysplasia in VMA.

Intramucosal versus submucosal tumor invasion

The most important factor to consider in the decision making is the depth of invasion of the cancer into the mucosal layers. Adenocarcinoma can be staged according to different depths of invasion (figure 1).¹⁴

Lymph node metastasis has not been reported in patients with HGD. Breaching the muscularis mucosa into the submucosa signifies the development of invasive cancer, where subsequent nodal involvement, distant metastasis and death can occur. In one study of 85 patients who had an oesophagectomy for mucosal or submucosal disease, there was no node involvement for any of the mucosal cancers, while 18% of submucosal cancers had a positive node, with the rate being higher if the cancer was poorly differentiated and there was lympho-vascular invasion (46%).¹⁵

This highlights the importance of a subtle change in the depth of vertical invasion, significantly increasing the risk of lymph node metastasis; hence identification of submucosal or invasive cancer is critical. Once deemed invasive, oesophagectomy is the only treatment offering a complete resection of the tumor as well as any involved lymph nodes, providing a complete cure of the disease if

localised to the region. Endoscopic ablative therapies are no longer appropriate and surgery is the preferred option, if the patient is fit.

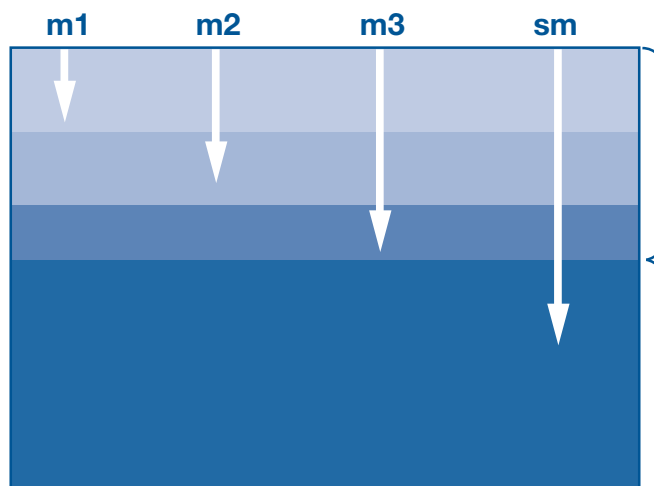
Endoscopic treatment of Barrett's Oesophagus and associated dysplasia

Endoscopic therapies include endoscopic mucosal resection (EMR), as well as multiple endoscopic ablative techniques developed in recent years, each differing in mechanism, efficacy, side-effects and cost effectiveness.

EMR, or mucosectomy, is the removal of affected mucosa by resection through the middle or deeper parts of the submucosa. The aim of EMR in dysplastic Barrett's and early oesophageal adenocarcinoma is to obtain a much better sample of the neoplasia for accurate pathological staging (depth of invasion) and grading (degree of differentiation). Where the lesion is focal, EMR may provide endoscopic cure so long as the lesion is confined to the mucosa, where the risk of lymph node metastasis is minimal. Both the "inject, suck, and cut" and "band and snare" techniques have been shown to yield equivalent and adequate depth of mucosa and submucosa.¹⁶ EMR appears to be an effective therapy achieving curative effect similar to surgery, but avoiding the mortality and morbidity. The potential for further change in the residual BO requires the residual mucosa to be ablated or intensive long-term endoscopic surveillance undertaken, given that there are few studies reporting the long-term outcomes from focal resection of these good prognostic pathologic entities.

Multiple methods of endoscopic ablation to eliminate the metaplastic or dysplastic epithelium in the oesophagus and induce reversion to normal squamous epithelium have been developed as a viable, oesophagus-sparing alternative for eligible patients. They include but are not limited to photodynamic therapy, argon plasma coagulation, cryotherapy, and most recently, radiofrequency ablation (RFA). Successful ablation has been achieved with each of these modalities, but inherent disadvantages impede their overall success. Photodynamic therapy, one of the first techniques established, has a high (77%) complete elimination rate of HGD when combined with proton pump inhibitors.¹⁷

Figure 1: Subdivision of mucosal cancer according to depth of invasion.



Intramucosal Involvement:

- m1: carcinoma in situ, within epithelial layer
- m2: cancer invasion into lamina propria
- m3: cancer infiltration into muscularis mucosa

Submucosal Involvement:

- sm1: into upper third of submucosa
- sm2: into middle third
- sm3: into lower third

But its drawbacks include strictures, odynophagia and cutaneous photo-toxicity. The repeated point-by-point application of argon plasma coagulation risks burying BO below neosquamous epithelium, limiting its use as a single mode therapy, but it is now often used as an adjuvant ablative therapy. Only a few uncontrolled studies have been conducted in an attempt to establish the role of cryotherapy in treatment of BO and dysplasia with promising results.¹⁸⁻²⁰ The HALO® RFA system (Barrx Medical, Sunnyvale, CA, USA) has yielded consistently better results than any alternate ablative therapy. The study with the most convincing result was a randomised control trial done by Shaheen et al among patients with low grade dysplasia and HGD. The advantages include minimal complications (strictures, bleeding), higher patient tolerability and higher rates of total ablation of BO with minimal chance of developing buried BO.²¹ Contemporarily, the results of RFA have been impressive, and a strategy of RFA with EMR for careful pre-ablative screening and staging is considered by many as the standard of endoscopic care.^{22,23} When HGD or intramucosal carcinoma (IMC) are to be managed endoscopically, any VMA should be removed with EMR, restricting the ablative techniques to the remaining 'normal' mucosa.

Oesophagectomy

Historically, for patients considered fit, an oesophagectomy has been considered the definitive treatment for HGD and IMC because the procedure completely eradicates the neoplastic mucosa, as well as removing the regional lymph nodes. In a review of 29 studies with 548 patients where an oesophageal resection was performed for HGD, the incidence of an occult carcinoma was 37%.²⁴ The cancer was deeper than the mucosa in more than 60% of those patients. In 2003, Korst and colleagues advocated resection for HGD as the treatment of choice unless the patient was unfit.²⁵ However, that study did not mention EMR. Since that time endoscopic techniques have evolved with better biopsy protocols and the use of directed EMR. We are now able to more carefully assess the extent of the HGD, as well as the potential for an associated area of carcinoma formation. Indeed it has been reported that in patients with HGD or early mucosal carcinoma, EMR can successfully obtain a complete resection of the disease at the time of the first treatment in 28% and up to 74% after repeated mucosal resections.²⁶

Centres performing a high volume of oesophageal resection report operative mortalities between 2-4% but rates of 0-1% have been reported when the resection was for HGD/IMC.²⁷ With the recent trend to minimally invasive approaches for oesophageal resection it has been hoped that the morbidity and mortality from the procedure may be reduced. To date there has been no clear evidence of a major difference in operative mortality or in the general outcomes comparing open approaches with minimally invasive approaches.^{27,28} Advocates for resection claim that the long term functional outcomes are at least equivalent to the general population.²⁹ However, patients do have higher incidences of a number of functional symptoms such as dumping syndrome, bloat, reflux and diarrhoea.³⁰

Clearly the major disadvantage of an oesophagectomy is the potential for early operative mortality. Treatment failure from various modalities of endoscopic therapy has been reported to be 6-20%, with the development of a new metachronous cancer in the at-risk mucosa.^{31,32} Zehetner et al compared the outcomes from patients who had an oesophageal resection for HGD/IMC (61 patients) with a cohort they treated using endoscopic therapy (40 patients).³² The morbidity from resection was 39% with no complications in the patients who had endotherapy. There were no procedure related deaths in either group. The overall survival at three years was 94% for both groups and the cancer-related survival at that time of 100% in both groups. However, the incidence of a new metachronous primary neoplastic lesion in the endotherapy group was 20%; there were no metachronous lesions after an oesophagectomy.

The group in Weisbaden, Germany, report complete resection rates from EMR for HGD and IMC to be 97%. Only a few patients had their residual Barrett's mucosa ablated (photodynamic therapy) leading to metachronous HGD or IMC in the at-risk residual Barrett's mucosa in 21%.³³ In this report, the risk factors for recurrence were identified to be piecemeal resection, long segment BO, no ablation of the BO, multifocal neoplasia and the time to complete removal of the identified lesion to be more than 10 months. This group highlighted the need to intensively follow patients with regular endoscopy and they have also used other imaging including EUS and CT scanning. The addition of ablative procedures such as RFA, should reduce the incidence metachronous lesions. Long-term follow-up studies after RFA will be important to establish the safety of local therapy in these carefully selected patients.

For IMC, there has been one comparative study assessing oesophagectomy compared with EMR and BO ablation. The group from Weisbaden compared the results of a cohort of patients with IMC treated with EMR and argon plasma coagulation to the non-dysplastic BO with a matched group of patients who had a resection performed in a high volume surgical unit in Cologne, during the same time period.³³ The major complication rate for surgery was 32% and the 90-day mortality 2.6%; with a median follow up of 4.1 years, there was no recurrence of the tumour locally or systemically. The patients who had endoscopic therapy had no major morbidity or mortality; within a median follow up of 3.7 months. 6.6% of patients needed further local therapies, with one patient not completely cleared locally because of death from an unrelated cause before total eradication of the BO was achieved.

The long-term results from the endoscopic therapies are not known and as previously stated, diligent regular follow-up endoscopy in these patients is essential. An operative death from surgery is a disaster, but equally a death from metastatic adenocarcinoma in a patient who had endoscopic therapy for a potentially curable disease is also a disaster. The decision to proceed with endoscopic therapy as the definitive treatment in a patient with HGD or IMC is not always clear-cut and should be made in a collaborative environment including the interventional

endoscopist and an oesophageal surgeon. The better oesophagectomy outcomes occur in specialist high-volume centres. However, the technical expertise of the surgeon is only one component in the operative and cancer outcomes for these patients. For endoscopic therapies, it is likely the better HGD/IMC eradication figures and procedural outcomes will occur in centres that have a specific interest in this problem with strict follow-up endoscopy protocols in a multi-disciplinary clinical environment.

Conclusion

The choice of operative versus non-operative therapy for BO with HGD/IMC has changed in the last few decades. In appropriately selected patients, endoscopic therapy is increasingly becoming the treatment of choice as it has the potential to achieve the same curative effect as surgery, with minimal invasiveness and low complication rates. Yet surgery remains the definitive choice for advanced HGD and early cancer with submucosal infiltration. Multidisciplinary assessment and planning are important to achieving optimal outcomes.

References

- Bresalier RS. Barrett's Esophagus and esophageal adenocarcinoma. *Annu Rev Med.* 2009;60:221-31.
- Modiano N, Gerson LB. Barrett's esophagus: Incidence, etiology, pathophysiology, prevention and treatment. *Ther Clin Risk Manag.* 2007;3(6):1035-145.
- Pohl H, Welch HG. The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence. *J Natl Cancer Inst.* 2005;97(2):142-6.
- Shaheen NJ, Crosby MA, Bozynski EM, Sandler RS. Is there publication bias in the reporting of cancer risk in Barrett's esophagus? *Gastroenterology.* 2000;119(2):333-8.
- Wani S, Falk GW, Post J, Yerian L, Hall M, Wang A, et al. Patients with non-dysplastic Barrett's esophagus have low risks for developing dysplasia or esophageal adenocarcinoma. *Clin Gastroenterology and Hepatol.* 2011 9:220-7.
- Reid BJ, Blount PL, Feng Z, Levine DS. Optimizing endoscopic biopsy detection of early cancers in Barrett's high-grade dysplasia. *Am J Gastroenterol.* 2000;95(11):3089-96.
- Weston AP, Sharma P, Topalovski M, Richards R, Cherian R, Dixon A. Long-term follow-up of Barrett's high-grade dysplasia. *Am J Gastroenterol.* 2000;95(8):1888-93.
- Schnell TG, Sontag SJ, Chejfec G, Aranha G, Metz A, O'Connell S, et al. Long-term nonsurgical management of Barrett's esophagus with high-grade dysplasia. *Gastroenterology.* 2001;120(7):1607-19.
- Odze RD. Barrett esophagus: histology and pathology for the clinician. *Nat Rev Gastroenterol Hepatol.* 2009;6:478-90.
- Orloff M, Peterson C, He X, Ganapathi S, Heald B, Yang YR, et al. Germline Mutations in MSR1, ASCC1, and CTHRC1 in Patients With Barrett Esophagus and Esophageal Adenocarcinoma. *JAMA.* 2011;306(4):410-419.
- Playford RJ. New British Society of Gastroenterology (BSG) guidelines for the diagnosis and management of Barrett's oesophagus. *Gut.* 2006;55(4):442.
- Wang KK, Sampliner RE. Updated guidelines 2008 for the diagnosis, surveillance and therapy of Barrett's esophagus. *Am J Gastroenterol.* 2008;103(3):788-97.
- Buttar NS, Wang KK, Sebo TJ, Riehle DM, Krishnadath KK, Lutzke LS, et al. Extent of high-grade dysplasia in Barrett's esophagus correlates with risk of adenocarcinoma. *Gastroenterology.* 2001;120(7):1630-9.
- Soetikno RM, Gotoda T, Nakanishi Y, Soehendra N. Endoscopic mucosal resection. *Gastrointest Endosc.* 2003;57(4):567-79.
- Barbour AP, Jones M, Brown I, Gotley DC, Martin I, Thomas J, et al. Risk stratification for early esophageal adenocarcinoma: Analysis of lymphatic spread and prognostic factors. *Ann Surg Oncol.* 2010;17:2494-2502.
- Abrams JA, Fedi P, Vakiani E, Hafezi D, Remotti HE, Lightdale CJ. Depth of resection using two different endoscopic mucosal resection techniques. *Endoscopy.* 2008;40(5):395-9.
- Overholt BF, Lightdale CJ, Wang KK, Canto MI, Burdick S, Haggitt RC, 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(4):488-98.
- Johnson MH, Eastone JA, Horwhat JD. Cryoablation of Barrett's esophagus: a pilot study. *Gastrointest Endosc.* 2005;62:842-848.
- Dumot JA, Vargo JJ 2nd, Falk GW, Frey L, Lopez R, Rice TW. An open-label, prospective trial of cryospray ablation for Barrett's esophagus high-grade dysplasia and early esophageal cancer in high-risk patients. *Gastrointest Endosc.* 2009;70(4):635-44.
- Greenwald BD, Dumot JA, Horwhat JD, Lightdale CJ, Abrams JA. Safety, tolerability, and efficacy of endoscopic low-pressure liquid nitrogen spray cryotherapy in the esophagus. *Dis Esophagus.* 2010;23(1):13-9.
- Shaheen NJ, Sharma P, Overholt BF, Wolfsen HC, Sampliner RE, Wang KK, et al. Radiofrequency ablation in Barrett's esophagus with dysplasia. *N Engl J Med.* 2009;360(22):2277-88.
- Gondrie JJ, Pouw RE, Sondermeijer CM, Peters FP, Curvers WL, Rosmolen WD, et al. Stepwise circumferential and focal ablation of Barrett's esophagus with high-grade dysplasia: results of the first prospective series of 11 patients. *Endoscopy.* 2008;40(5):359-69.
- Pouw RE, Wirths K, Eisendrath P, Sondermeijer CM, Ten Kate FJ, Fockens P, et al. Efficacy of radiofrequency ablation combined with endoscopic resection for Barrett's esophagus with early neoplasia. *Clin Gastroenterol Hepatol.* 2010;8(1):23-9.
- Williams VA, Watson TJ, Herbelle FA, Gellersen O, Raymond D, Jones C, et al. Esophagectomy for high grade dysplasia is safe, curative and results in good alimentary outcome. *J Gastrointest Surg.* 2007;11:1589-97.
- Korst RJ, Altorki N. High grade dysplasia: Surveillance, mucosal ablation or resection? *World J surg.* 2003;27:1030-1034.
- Vieth M, Ell C, Gossner L. Histological analysis of endoscopic resection specimens from 326 patients with Barrett's esophagus and early neoplasia. *Endoscopy.* 2004;36:776-781.
- Low DE. Update on staging and surgical treatment options for esophageal cancer. *J Gastrointest Surg.* 2011;15:719-729.
- Smithers BM. Minimally Invasive Esophagectomy. *Expert Rev Gastroenterol Hepatol.* 2010;4:91-99.
- Headrick JR, Nicols FC, Miller DL, Allen MS, Trastek VF, Deschamps C, et al. High-grade esophageal dysplasia: long term survival and quality of life after esophagectomy. *Ann Thorac Surg.* 2002;73:1697-1702.
- Moraca RJ, Low DE. Outcomes and health-related quality of life after esophagectomy for high-grade dysplasia and interamucosal cancer. *Arch Surg.* 2006;141:545-549.
- Das A, Singh V, Fleischer DE, Sharma VK. A comparison of endoscopic treatment and surgery for early esophageal cancer: An Analysis of surveillance epidemiology and end results data, *Am J Gastroenterol.* 2008;103:1340-1345.
- Zehetner J, DeMeester SR, Hagen A, Ayazi S, Augustin F, Lipham JC, et al. Endoscopic resection and ablation versus esophagectomy for high-grade dysplasia and intramucosal carcinoma. *J Thorac Cardiovasc Surg.* 2011;141:39-47.
- Pech O, Behrens A, May A, Nachbar L, Gossner L, Rabenstein T, 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.