

# ADVANCES IN ENDOSCOPY

Current Developments in Diagnostic and Therapeutic Endoscopy

Section Editor: John Baillie, MB ChB, FRCP

## Endoscopic Resection of Barrett Esophagus With High-Grade Dysplasia and Early Esophageal Cancer

Michael J. Bourke, MBBS, FRACP  
Director of Gastrointestinal Endoscopy  
Department of Gastroenterology and Hepatology  
Westmead Hospital  
Sydney, Australia

**G&H** You recently published a study on endoscopic resection of Barrett esophagus with high-grade dysplasia and early esophageal cancer. Where was the study conducted?

**MB** The study, which was published in a recent issue of the *American Journal of Gastroenterology*, was conducted in Westmead Hospital in Sydney, Australia and Princess Alexandra Hospital in Brisbane, Australia, which are large tertiary referral centers of 1,000 beds and 600 beds, respectively. Both sites have advanced endoscopy units that specialize in managing complex and tertiary referral cases. Patients with complex or specialized endoscopic problems are referred from both community gastroenterologists and other teaching hospitals. Each year, the Westmead center performs 1,000 endoscopic retrograde cholangiopancreatographies, 500 endoscopic ultrasounds (EUS), and more than 400 complex endoscopic resections (ER) for mucosal neoplasia, including high-grade dysplasia (HGD) and early adenocarcinoma (EAC) in Barrett esophagus, duodenal and ampullary adenomas, and, in particular, large sessile polyps and laterally spreading tumors of the colon. Patients referred with these types of pathologies are invited to participate in prospective studies designed to assess, enhance, and validate the safety and efficacy of ER for mucosal neoplasia. The unit holds small group educational events focused on lesion recognition, assessment, and endoscopic therapy, as well

as an annual live endoscopy course with an invited international faculty.

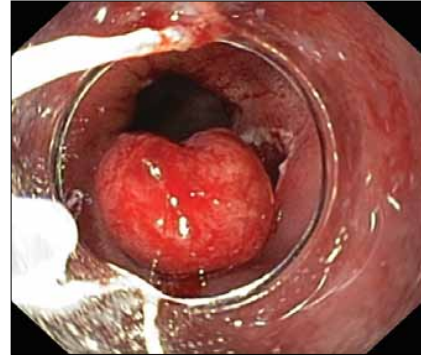
**G&H** What were the concept and methodology of your study?

**MB** Soon after we began performing ER for staging and potential therapy for Barrett HGD and early mucosal cancer at our centers, we designed this study. At that time, based upon our previous experience of referring patients for surgery, we had a suspicion that the current methods for staging Barrett HGD were fairly inaccurate. In addition, it was well known that esophagectomy was a fairly morbid procedure associated with significant mortality, even in high-volume centers. Thus, we designed the study to prospectively assess the influence of ER on histologic grading and tumor staging, as well as to examine the long-term outcomes of endoscopic therapy for HGD, early cancer, and complete Barrett excision (CBE).

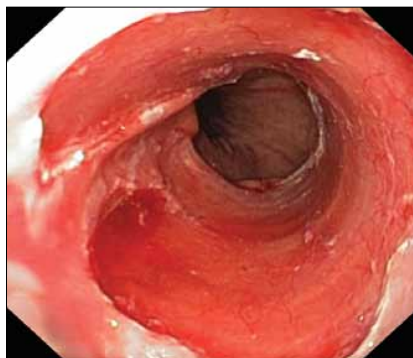
We prospectively recorded prior biopsy histology, endoscopic morphology, and outcomes in patients referred to our 2 centers for endoscopic assessment and management of biopsy-proven HGD or EAC. All patients entering the study had histologically confirmed HGD or EAC. Seventy of the 75 patients underwent prior diagnostic endoscopy at 1 of the 2 centers to intensively assess and histologically map the Barrett segment, including 4-quadrant biopsies at 1-cm intervals using large-cup forceps and targeted biopsies of any mucosal irregularity or nodules. Five patients with nodules proceeded directly to ER, though the prior histology was reviewed in-house. Two specialized gastrointestinal histopathologists reviewed all of the biopsy slides and determined the pre-ER biopsy grade and stage. Initially, all patients underwent pre-ER staging with computed tomography (CT) and EUS, but after 2005, given the limited utility of CT and EUS for staging these early lesions in our experience, these



**Figure 1.** Circumferential Barrett segment of 2–3 cm with histologically proven high-grade dysplasia.



**Figure 2.** Radical mucosectomy by the multiband technique.



**Figure 3.** Circumferential resection of 80%, requiring follow-up excision of residual Barrett mucosa in 6–8 weeks.



**Figure 4.** Retroflex view in the stomach showing 80% circumferential excision onto gastric mucosa.

tests were omitted from the routine protocol and were required only if the endoscopic appearance was suspicious for invasive adenocarcinoma (lesion >20 mm, ulcerated, or depressed—Paris classification 0-IIc). Early in the study period, the cap technique was used for ER, but we changed to multiband mucosectomy (MBM) when we became convinced of its superior technical ease and safety. More than two thirds of the resections were performed via this technique. ER specimens were assessed histologically by the same pathologists who were blinded to the initial histopathology results. Finally, comparisons could thus be made between grade and stage in the pre-ER diagnostic biopsy specimens versus the ER specimens. Patients with submucosal invasion were referred for surgical evaluation. Following ER, surveillance endoscopy consisted of assessment by narrow-band imaging and acetic acid spray with 4-quadrant biopsies every 1 cm of the Barrett segment and targeted biopsies of the ER scar

performed at 3, 6, and 12 months after the initial ER, and then annually.

CBE by ER was offered in patients who had Barrett segments 3 cm or less, limited comorbidity, and were less than 75 years of age. Radical mucosectomy was performed with the initial resection, including removal of the target lesion and further ER, ultimately involving a 50–80% circumferential resection. Endoscopy was repeated every 6–8 weeks until CBE was achieved. CBE was defined as the endoscopic and histologic absence of Barrett mucosa. Figures 1–4 show Barrett esophagus during these stages before and after ER.

#### **G&H** What were the results of this study?

**MB** ER for HGD (89%) or EAC (11%) was performed in 75 patients with Barrett segments 1–16 cm in length (mean, 3.6 cm). The endoscopic appearance was flat and

inconspicuous in one third of patients, mucosal irregularity in another third of patients, and a nodule in 27% of patients. Three quarters of the procedures were performed with MBM. Technical success was achieved in 100% of cases. The total number of ER sessions ranged from 1 to 5, but 85% of patients had 2 or fewer sessions.

When compared to pre-ER biopsy histology, histologic assessment of the ER specimen resulted in a change in grade or stage in 48%, consisting of downgrading/staging in 28% and upgrading/staging in 20%. Post-ER diagnoses included the full spectrum of pathology, ranging from no dysplasia to submucosal invasive adenocarcinoma, including a total of 23% with either no dysplasia or low-grade dysplasia.

Complications were minimal, with immediate bleeding requiring endoscopic intervention (which should be seen as part and parcel of the procedure) in 10%. One of these patients required 2 nights of hospitalization after aspiration of blood, but the patient recovered completely. Two patients had narcotic analgesia for postprocedural chest pain, with same-day discharge. Nearly all patients were discharged on the day of their procedure. There were no perforations. Among the CBE group (35 patients), 17% of patients developed functionally significant strictures that required a total of 13 dilatations for the entire group.

In all, 17 patients had adenocarcinoma (10 mucosal/7 submucosal invasion). All of the submucosal invasion patients were referred for surgery. Those with mucosal adenocarcinoma (lamina propria invasion only) were managed endoscopically. Of the 7 patients referred for surgery, surgery was declined because of patient choice in 2 patients and comorbidities in 2 other patients. These 4 patients underwent further endoscopic management: 2 were successfully treated with CBE, and 2 were treated with radiotherapy (though 1 died because of radiation pneumonitis). Thus, only 3 patients were treated surgically, 2 of whom had no carcinoma in the esophagectomy specimen and a third patient who had a T1N0M0 lesion.

CBE was successful in all patients who completed the protocol and was achieved in a mean of 2 sessions (range, 1–3 sessions). One patient was found to have submucosal invasive adenocarcinoma and was referred for surgery (no malignancy was found in the surgical specimen), and another patient developed a comorbidity, which precluded further endoscopic treatment.

The mean follow-up for CBE cases was 31 months (range, 3–68 months). No patient with CBE developed metachronous HGD or EAC, nor was there any recurrent Barrett mucosa or “buried glands”/“buried Barrett” during intensive endoscopic surveillance. In contrast, the mean follow-up for the non-CBE cases was 31 months (range, 3–89 months). Eight of the 35 non-CBE patients developed metachronous lesions (23%). In total, 4

patients died during follow-up (aged 92 years, 88 years, 83 years, and 81 years), with no deaths attributable to Barrett adenocarcinoma.

The Kaplan-Meier 5-year survival rate was 89%, and survival at 50-month follow-up was 97%.

### G&H What did the study conclude, and what messages can other centers performing Barrett mucosa excision take away from it?

**MB** We concluded that ER alters histologic grade or local T stage in 48% of patients and dramatically reduces esophagectomy rates by providing safe and effective therapy. In addition, we concluded that treatment strategy based upon biopsy histology, without ER staging, may result in unnecessary surgery, greatly enhancing treatment cost and creating unnecessary short- and long-term morbidity and potential perioperative mortality. Also, approximately 25% of patients will develop significant metachronous lesions in the residual Barrett segment over the ensuing 3-year period, thus making elimination of the residual Barrett segment necessary. Finally, we concluded that ER has a high success rate (94%) for CBE in short-segment Barrett esophagus with limited complications and a low and endoscopically amenable stricture rate without long-term sequelae when performed with careful technique.

### G&H What were the limitations of the study?

**MB** Ideally, a large multicenter randomized trial comparing ER, radiofrequency ablation (RFA), and esophagectomy is required to establish the optimal treatment modality for HGD or EAC within short- or long-segment Barrett esophagus, but our work, and that of others, is fairly compelling. Surgery always remains a viable backup option and is not precluded by prior endoscopic therapy. Ultimately, the most effective treatment option may differ between short- and long-segment disease.

### G&H What does training entail for endoscopists who wish to learn this type of Barrett ablation? Is there an unmet need?

**MB** The basic technical skills for performing simple single band or MBM in the esophagus are not difficult. However, significant experience and more advanced training is required to develop satisfactory skills in lesion assessment, extended MBM, CBE for short-segment disease, and the endoscopic management of complications after ER. Thus, to obtain a high-quality practice in Barrett ER, there are 2 prerequisites: training within an advanced endoscopy fellowship or the equivalent with a significant Barrett dysplasia and early neoplasia case load; and a current or future practice in a tertiary refer-

ral center with a significant pool of referrers draining an estimated population of 500,000–1,000,000 individuals.

Although Barrett esophagus is not infrequent (with an overall general community prevalence of approximately 1.5%), HGD and EAC are quite uncommon. Overwhelmingly, the vast majority of patients with Barrett esophagus will not develop nor succumb to esophageal cancer. Cardiovascular events remain the single most important causes of significant morbidity and mortality in this cohort. In fact, one could argue that, when a diagnosis of Barrett esophagus is established, the most important steps are to: assess for and treat cardiovascular risk factors (hypertension, hypercholesterolemia, obesity, and so on); initiate proton pump inhibitor therapy; consider aspirin for primary cardiovascular prevention; and offer at least 1 early surveillance endoscopy, as most neoplasia occurs within the first 1–2 years after diagnosis, with the risk declining significantly after that point. Therefore, endoscopic treatment for nondysplastic Barrett outside of carefully controlled scientific trials currently cannot be justified.

### G&H What areas require further research in Barrett esophagus?

**MB** The obvious deficits in our knowledge base are a complete understanding of the natural history of Barrett esophagus and better endoscopic therapies. We urgently need some form of biomarker, either serologic, tissue-based, or a combination that, with demographic factors, is able to stratify individuals according to the risk of neoplastic progression. The ability to stratify the risk of progression would allow for better selection of patients for surveillance, in particular those who require intensive surveillance and those who will not benefit from surveillance at all. The reduction in unnecessary screening endoscopy would result in large cost savings and enhance clinical outcomes. Patients at high risk could be offered prophylactic therapy.

There is a strong need for more effective endoscopic therapies for complete elimination of Barrett mucosa, as all of our current therapies have limitations. For example, RFA is attractive because of its technical ease and lack of

complications, but it is not an excisional therapy; thus, complete histology is not available, and significant neoplasia may be missed even in carefully designed prospective trials. In addition, the long-term outcomes of RFA are unknown, and many patients have “buried glands” post-RFA. At present, the implications of “buried glands” are not clear, and whether they may become dysplastic remains unknown. Nevertheless, RFA is currently the best option for patients with dysplastic long-segment disease.

Another example of endoscopic therapy with limitations is endoscopic submucosal dissection (ESD), with which we have only limited experience. ESD has the advantage of achieving en bloc excision, but it is technically challenging. Given the pathology of Barrett mucosa, a histologic R0 excision is less frequently achieved than for other forms of gastrointestinal neoplasia removed after ESD. Also, the incidence of refractory post-ESD esophageal strictures is almost universal.

Finally, two-stage radical mucosectomy by MBM is a highly effective therapy for short segments ( $\leq$ C3 M4-5) in experienced hands, providing complete histology (albeit, in piecemeal format). The major drawback is a stricture rate between 15–50%. This rate increases in prevalence with the length of the segment excised. When performed well, the risk of residual Barrett islands (which are usually small and easily treated by thermal means, eg, argon plasma coagulation) is negligible and, in our experience, subsquamous “buried glands” are absent.

### Suggested Reading

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