Chapter 22
Optimal Therapy for Barrett High Grade Dysplasia

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Abstract The management of Barrett's esophagus with high-grade dysplasia has undergone an evolution from prophylactic esophagectomy to an organ sparing approach based on endoscopic therapies that have emerged over the recent years. Esophagectomy is now reserved only for selected cases of patients with high-grade dysplasia and intramucosal carcinoma in Barrett's esophagus. This chapter outlines terminology, the appropriate assessment, the management strategy, and the options of therapy for patients with Barrett's esophagus with high-grade dysplasia.

Keywords Barrett's esophagus • High grade dysplasia • Esophagectomy • Endoscopic mucosal resection • Ablation

Abbreviation

BE	Barrett's esophagus
CT	Computed tomography
EUS	Endoscopic ultrasound
GI	Gastrointestinal
HGD	High-grade dysplasia
IMC	Intramucosal carcinoma
LNM	Lymph node metastasis

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Introduction

Esophageal adenocarcinoma (EAC) is an increasingly prevalent cancer and caries a dismal prognosis when diagnosed at advanced stages, on the order of 20 % 5-year survival [1, 2]. Barrett's esophagus (BE) is a risk factor for EAC, and is rapidly increasing in incidence throughout the United States [3]. BE occurs when the normal squamous lining of the esophagus undergoes conversion to specialized intestinal, columnar epithelium. Given the 30-fold increase in risk over the general population [4], patients with BE have been targeted for surveillance programs. The detection of high-grade dysplasia (HGD) in patients with BE offers the best marker to identify who is at risk for EAC and represents a point of intervention to cure or prevent EAC. The standard of care has shifted from managing these patients with prophylactic esophagectomy to esophageal sparing approaches that have incorporated emerging endoscopic therapies. This chapter will outline relevant classification terminology, appropriate assessment, management strategies, and options for therapy for patients with BE with HGD.

Search Strategy

This chapter is based on a search of the literature with Medline, PubMed, and selected references using key words Barrett's esophagus, high-grade dysplasia, endoscopic mucosal resection, esophagectomy, and ablation from the years 1988 to 2013. The patient population is focused on patients with Barrett's esophagus with HGD. There is also attention given to patients with intramucosal carcinoma (IMC) as some studies have incorporated both patient populations and HGD and IMC have some similarities in management. Interventions investigated include esophagectomy, endoscopic mucosal resection, radiofrequency ablation, photodynamic therapy, and cryotherapy. Outcomes were based on survival and remission of neoplasia.

Background

Classification

BE is an endoscopic and pathologic diagnosis. Endoscopically, the squamocolumnar junction is detected proximal to the top of the gastric folds with the observation of salmon colored mucosa seen in the tubular esophagus. In the United States BE is defined any length of columnar lined esophagus with intestinal metaplasia, yet there is lack of universal agreement on whether intestinal metaplasia (defined by the presence of goblet cells) is necessary for a diagnosis of BE. In Britain and Japan,

the presence of goblet cells is not necessary for a diagnosis of BE. Furthermore a small percentage of adult patients with columnar metaplasia do not contain goblet cells, the chances of detecting goblet cells is proportional to the length of columnar mucosa sampled, sampling error exists, and the presence of goblet cells can wax and wane over the course of BE [5].

The histopathologic diagnosis of BE may be classified into three categories: BE without dysplasia, BE with low-grade dysplasia (LGD), and BE with HGD. Dysplasia is defined as neoplastic cytological and architectural atypia without evidence of invasion past the basement membrane. Carcinoma in situ and HGD are equivalent, and for the purposes of this discussion, the term HGD will be used. Unfortunately, interobserver agreement between expert pathologists is suboptimal due to small biopsy size, lack of consensus on boundaries demarcating degrees of dysplasia, and difficulty discerning dysplasia from inflammation [6].

IMC is defined as neoplasia that extends beyond the basement membrane and into the lamina propria. IMC carries a minimal nodal metastasis risk of less than 5 % [7–9]. The risk of lymph node metastasis relates to differentiation, depth of tumor, lymphatic, vascular, or neural involvement. Submucosal carcinoma invades the submucosa, but not the muscularis propria, and carries a >20 % lymph node metastasis risk [8]. A peculiarity to Barrett's esophagus is the presence of duplicated muscularis mucosa. If not recognized or accounted for, this may lead to overstaging of tumor that may involve the superficial bundle of muscularis mucosa but not the deeper bundle as submucosal carcinoma when it may only be IMC [10, 11]. The identification of BE in the stages of intestinal metaplasia, LGD, HGD, IMC and submucosal carcinoma has profound treatment implications based on their dramatically different prognostic profiles [12].

Appropriate Assessment of Patients with Barrett's Associated Neoplasia

It is critical to confirm all dysplasia with an expert gastrointestinal pathologist as considerable disagreement in the diagnosis of dysplastic BE exists, and this diagnosis has profound treatment and outcome implications. Curvers et al. found that 85 % of patients diagnosed with LGD in six non-university hospitals between 2000 and 2006 were down-staged to non-dysplastic BE or indefinite for dysplasia after histology review by two expert pathologists. After a mean follow up of 51 months, the patients with confirmed LGD in this study had a cumulative risk of progressing to HGD or EAC of 85 % at 109.1 months compared to 4.6 % in 107.4 months for patients down-staged to non-dysplastic BE [13].

A careful endoscopic examination of the Barrett's segment is paramount to detect dysplasia. Visible lesions in the setting of HGD are at high risk of harboring cancer. Visible lesions may be obvious in the cases of protruding lesions or ulcers, but may also be subtler in nature with slight elevations, depressions, or flat appearing

mucosa. The traditional surveillance strategy for BE is the Seattle protocol, with targeted biopsies of all visible lesions followed by four quadrant random biopsies every 1–2 cm of the Barrett's segment [14, 15]. However, dysplastic lesions can still be missed on biopsy given the patchy and focal nature of dysplasia, sampling error, and poor adherence to the Seattle protocol, which increases sampling error and risk of missed dysplasia [16]. A detailed exam utilizing high definition white light endoscopy (WLE) is essential in the recognition of lesions. Additional imaging modalities which may improve the detection of neoplasia include magnification endoscopy [17], chromoendoscopy [18], narrow band imaging [19] and confocal laser endomicroscopy [20].

Any mucosal irregularity warrants an endoscopic mucosal resection (EMR), since endoscopically visible lesions in the setting of HGD are associated with a high risk of occult cancer. Mucosal resection of visible lesions provides accurate depth staging and visualization of lateral margins. Chennat et al. found that 14 % of cases were upstaged and 31 % down-staged after endoscopic mucosal resection compared to pre-treatment biopsies [21]. Endoscopically resected specimens allow for greater interobserver agreement between pathologists than standard biopsy specimens [22].

Endoscopic ultrasound and CT help determine tumor depth and regional lymph node metastasis. EUS has improved accuracy for tumor depths at more advanced stages, but has difficulty distinguishing between IMC and submucosal cancer [23]. Therefore, for superficial Barrett's associated neoplasia, EMR is used for depth staging and the role of EUS with fine needle aspiration focuses on detection of nodal metastasis [24].

Rationale for Intervention

The incidence of EAC in patients with non-dysplastic BE was previously thought to be 0.5 % per person per year, but now appears closer to 0.3 % per person per year [25]. HGD is the best marker to identify which patients with BE are at risk of progressing to EAC. It is estimated that 6–20 % of patients with HGD develop EAC within 17–35 months of follow up based on a prospective study [26]. Rastogi et al. found that patients with HGD developed EAC with an average incidence of 6 of every 100 patients per year during the first 1.5–7 years of endoscopic surveillance [27].

There has been an evolution in management strategy for patients with Barrett's associated neoplasia. Traditionally, patients without dysplasia or LGD underwent surveillance. Patients with cancer underwent esophagectomy and/or systemic therapy, and patients with HGD had two radically different options, surveillance or esophagectomy. The surgical literature reported rates of prevalent occult cancer among patients who underwent a prophylactic esophagectomy for the management of HGD ranging from 0 to 73 % [28–30], with an assumed risk of patients with HGD harboring occult invasive EAC estimated to be 40 % [31]. This high risk of

prevalent occult cancer supported the rationale for prophylactic esophagectomy in patients with HGD.

A systematic review analyzed the risk of EAC in 441 patients with HGD who underwent esophagectomy and found that, while the pooled average rate of occult adenocarcinoma was 39.9 %, the rate of proven invasive cancer (defined by submucosal invasion or beyond) was only 12.7 % [9]. Most patients in this study were found to have IMC, which carries a 3 % risk of nodal metastasis and is amenable to endoscopic therapy [8, 9, 32]. It is estimated that 80–100 % of patients with HGD can be successfully treated with endoscopic eradication therapy [33] and complete removal of BE with intestinal metaplasia occurs in >75 % of cases [34]. Given that the risk of mortality after esophagectomy is 3–4 % [35], the pursuit of endoscopic therapy may offer an appropriate balance of risks and benefits.

Endoscopic Treatment Approaches

Endoscopic treatment of BE begins with endoscopic resection of visible lesions in the setting of neoplasia, followed by treatment of the remainder of the Barrett's epithelium. These treatment modalities are divided into tissue acquiring and non-tissue acquiring modalities. Tissue acquiring methods include focal EMR, circumferential EMR, and endoscopic submucosal dissection (ESD). Non-tissue acquiring modalities include photodynamic therapy, radiofrequency ablation, and cryotherapy. Visible lesions in patients with BE should be treated with a tissue acquiring modality so that lesions can be appropriately staged and resected. After all areas of localized neoplasia are removed, the remainder of the Barrett's epithelium can be eradicated by non-tissue acquiring modalities in order to treat metachronous or synchronous lesions.

Tissue-Acquiring Ablative Therapies

Endoscopic Resection

EMR removes affected mucosa through the deeper part of the submucosa in a piecemeal or en bloc fashion. It can be performed via band ligation, free hand, lift-and-cut, or cap technique. The primary functions of EMR are to obtain a specimen that allows for accurate histopathologic staging/grading as well as endoscopic treatment. EMR can be performed focally or for the entirety of Barrett's epithelium. Focal EMR is an acceptable technique for patients with low-risk and early lesions with complete remission rates of 97–100 % [36]. Unfortunately, focal EMR, when used a sole modality, has high recurrence rates (14–47 %) [37]. Circumferential EMR, on the other hand, eradicates the entire length of Barrett's epithelium and has complete response rates of 76–100 % [21, 38]. Complications of EMR include bleeding, perforation, and stricture formation.

ESD is a technique in which dissection along the submucosal layer is performed with an endoscopic knife, allowing for resections of larger lesions (over 1.5 cm) and more accurate histopathological assessments. En bloc resection rates associated with ESD are greater than 90 %, and local recurrence rates after ESD are low (0–3.1 %) [39]. This compares favorably with the local recurrence rates of EMR which are approximately 20 %, likely secondary to piecemeal resections [40]. ESD remains a technically challenging procedure requiring specialized training that is not yet performed with great frequency outside of east Asian nations.

Non-tissue Acquiring Modalities

Radiofrequency Ablation

RFA applies direct thermal energy to the mucosal lining circumferentially with a balloon catheter or in a focal fashion. During the procedure, areas of mucosa are directly applied with thermal energy via electrodes embedded on the balloon or focal device. In a randomized trial performed by Shaheen et al. patients with HGD treated with RFA had an 81 % complete eradication rate compared to 19 % of controls that received a sham procedure. 77.4 % of patients in the ablation group had complete eradication of intestinal metaplasia, compared with 2.3 % in controls. The RFA group had lower rates of progression (3.6 % vs. 16.3 %) and fewer cancers (1.2 vs. 9.3 %). Complete remission of intestinal metaplasia was persistent in 92 % of patients at 5 years [41]. Complications include non-cardiac chest pain, lacerations, and stenosis. RFA has decreased complication rates of bleeding and stenosis compared to EMR. Expert opinion suggests that RFA is the best available ablation technique for the treatment of flat HGD and for eradication of residual BE after focal EMR [34].

Cryotherapy

Cryotherapy uses a low-pressure spray catheter to deliver liquid nitrogen to a targeted area in order to freeze the epithelium to a depth of 2 mm. The freezing and subsequent thawing causes ischemic necrosis. Sessions can be repeated every 4–6 weeks and requires a decompression tube in the esophagus to prevent over-inflation and perforation. Recent studies showed initial success with regression of HGD in 94–97 % [42, 43]. Cryotherapy was also studied in 30 patients with HGD and IMC who were not surgical candidates, resulting in a 90 % rate of histologic down staging and 30–40 % of patients experiencing complete resolution of dysplasia. At 1-year, elimination of cancer or down staging was achieved in 68 % of HGD and 80 % of IMC patients [44].

Photodynamic Therapy

In photodynamic therapy (PDT) an intravenous photo sensitizer binds to dysplastic tissue and 2–3 days later an endoscopic delivery of laser light occurs, which

produces oxygen radicals and triggers cell death [45]. A retrospective analysis of patients with HGD who received PDT or esophagectomy revealed no significant differences in mortality or long-term survival based, yet found that management of IMC with PDT is less efficacious than other treatment modalities [35]. Complications of PDT include decreased efficacy compared to newer therapies due to the presence of buried glands containing foci of BE after therapy, cutaneous photo-toxicity, and stricture formation. These drawbacks have limited the use of PDT in the current era.

Hybrid Therapy

Hybrid therapy of EMR and RFA, with resection of visible mucosal irregularities via EMR followed by ablation of all intestinal metaplasia with RFA, may be the endoscopic modality of choice. A study performed by Kim et al. including 169 patients with BE and advanced neoplasia, found that EMR followed by RFA achieved complete eradication of dysplasia and complete eradication of intestinal metaplasia in 94 and 88 % of patients respectively, compared with 82.7 and 77.6 % of patients in the RFA only group. The complication rates between both groups were also similar [46].

Follow up

While complete eradication of BE possible, life-long surveillance with biopsies throughout the entire eradicated area is required to monitor for buried glands and the recurrence of neoplasia. Surveillance occurs with targeted biopsies of every suspicious lesion followed by 4-quadrant biopsies every 1–2 cm [34]. The cumulative incidence of recurrent intestinal metaplasia is nearly 32 % following complete eradication of Barrett's epithelium by RFA [47–49]. While median disease free survival for endoscopic therapy and esophagectomy appear equal, higher rates of metachronous and synchronous lesions are found following endoscopic therapy, again highlighting the importance of frequent endoscopic surveillance [50].

Biopsy intervals are typically based on the highest degree of dysplasia prior to ablation. Risk factors for recurrence include long segment BE, piecemeal resection by EMR, and multifocal disease [51]. All endoscopic therapy of BE is accompanied by concomitant lifelong PPI therapy.

Esophagectomy

Until the past decade, esophagectomy was the standard of care for BE with HGD or IMC, but now is reserved for select individuals with submucosal invasion, which carries an approximate 20 % risk of nodal metastasis [52], evidence of lymph node metastasis, or unsuccessful endoscopic therapy. Selected patients with HGD or IMC

with high-risk features may also benefit from surgery [53]. High-risk features may include gross characteristics including ulcerated/polypoid lesions, long segment BE, and lesions larger than 2 cm or histological characteristics including poor tumor differentiation, vascular, neural, lymphatic invasion, or multifocal HGD [53, 54].

The most important rationale for esophagectomy is its ability to completely resect the affected area, remove all associated lymph nodes, and afford a potential curative measure. Surgery allows for the most accurate staging and assessment of adequacy by looking for negative margins and lymph nodes. Complete resection minimizes the risk of metachronous lesions, which develop in residual Barrett's. With surgical resection, patients with HGD experience 5 year survival rates of over 90 % [55, 56].

The mortality rate associated with esophagectomy ranges between 1.5 and 15 %, while morbidity is as high as 50 % [57–60] When outcomes were controlled by hospital volume, institutions performing more than ten procedures per year had a significant difference in both post-operative mortality and post-operative complications. High volume centers with greater surgical expertise have decreased mortality rates of approximately 2–3 %, yet morbidity remains high [61, 62].

The complications experienced by 30–50 % of patients undergoing esophagectomy include dumping, anastomotic structuring, hemorrhage, anastomotic leak, infection, nerve palsy, pulmonary complications, regurgitation, diarrhea, and reflux [63, 64]. Both transhiatal and transthoracic esophagectomy techniques are performed in the United States. Transhiatal resections without thoracotomy can prevent respiratory compromise [65]. Transthoracic approaches may provide improved lymph node retrieval [66].

Minimally invasive, vagal sparing esophagectomy carries decreased perioperative morbidity, lower incidence of pulmonary complications, faster postoperative recovery, and shorter hospital stay when compared to transhiatal or en bloc esophagectomy. Unfortunately, the lymph node retrieval is inferior for this procedure. Peyre et al. demonstrated lower infectious, respiratory, and anastomotic complications in patients with HGD or IMC undergoing this procedure compared with transhiatal esophagectomy. The reduced post-vagotomy dumping and diarrhea, as well as shorter hospital stay appear to translate to improved quality of life [67].

It must also be noted that most studies describe outcomes after surgery for cancer and not HGD. Patients with cancer tend to be more debilitated preoperatively, and comorbid diseases are less frequent in patients with HGD alone [68]. Esophagectomy performed specifically for HGD has a pooled mortality of 1 % [68], making it a significantly lower risk procedure than when performed for EAC.

Endoscopic therapy for patients with HGD/IMC has a long-term survival similar to esophagectomy [35]. A retrospective study performed by Zehetner et al. compared 40 patients with HGD/IMC and 61 esophagectomy patents, and found that endoscopic therapy was associated with lower morbidity and similar 3-year survival rates, although multiple endoscopic procedures were necessary [69]. A retrospective study investigating 132 endoscopically treated patients and 46 surgically treated patients at the Mayo Clinic revealed similar mortality rates (17 and 20 % respectively), as well as overall survival. There was an increased rate of recurrent

carcinoma in the endoscopically treated cohort, yet all of these patients were successfully re-treated without impact on overall survival [70]. Additional long-term data and comparative data for minimally invasive surgical approaches and endoscopic approaches are needed for the indication of HGD/IMC to better determine what role esophagectomy should play for these patients.

Recommendations

The presence of dysplasia should be confirmed by a gastrointestinal pathologist. Endoscopic resection of mucosal irregularities in the setting of dysplasia in Barrett's esophagus should be performed for accurate T staging of neoplasia. Patients with Barrett's esophagus with high-grade dysplasia should be managed with endoscopic eradication therapy rather than surveillance. Esophagectomy should be reserved for patients with Barrett's associated neoplasia with submucosal invasion, lymph node metastasis, or failure of endoscopic therapy. Esophagectomy should be performed at high volume centers.

Conclusions

Barrett's associated neoplasia has undergone a paradigm shift in recent years. Figure 22.1 demonstrates the current standard approach that applies to most patients with Barrett's associated neoplasia. It is critical to confirm dysplasia with an expert GI pathologist and accurately stage superficial lesions with endoscopic resection. Most experts agree that HGD poses a sufficient risk for malignancy that intervention is warranted [33]. Given these intermediate term results and the minimal lymph node metastasis risk, endoscopic treatment is now standardly offered to patients with HGD and IMC. Currently, the American Gastroenterological Association and American Society for Gastrointestinal Endoscopy both recommend that endoscopic eradication therapy is preferred over surveillance for patients with confirmed HGD and IMC [34]. Given the mortality and morbidity of esophagectomy, surgical resection should be reserved for submucosal invasion, lymph node metastasis, and failure of endoscopic therapy. There may also be selected individuals with high-risk features of Barrett's associated neoplasia that may benefit from esophagectomy over endoscopic therapy; however future studies, longer-term data, and development of risk stratification approaches are required to further define that subset. Patients with Barrett's associated neoplasia should be counseled on all available options, and some may benefit from counseling by both a surgeon and an endoscopist. Ultimately, patients with HGD and IMC in Barrett's esophagus benefit from a multidisciplinary team approach where surgeons, endoscopist and pathologists are working in concert to leverage diagnostic accuracy, treatment efficacy, mitigation of risks and quality of life for patients with Barrett's associated neoplasia.

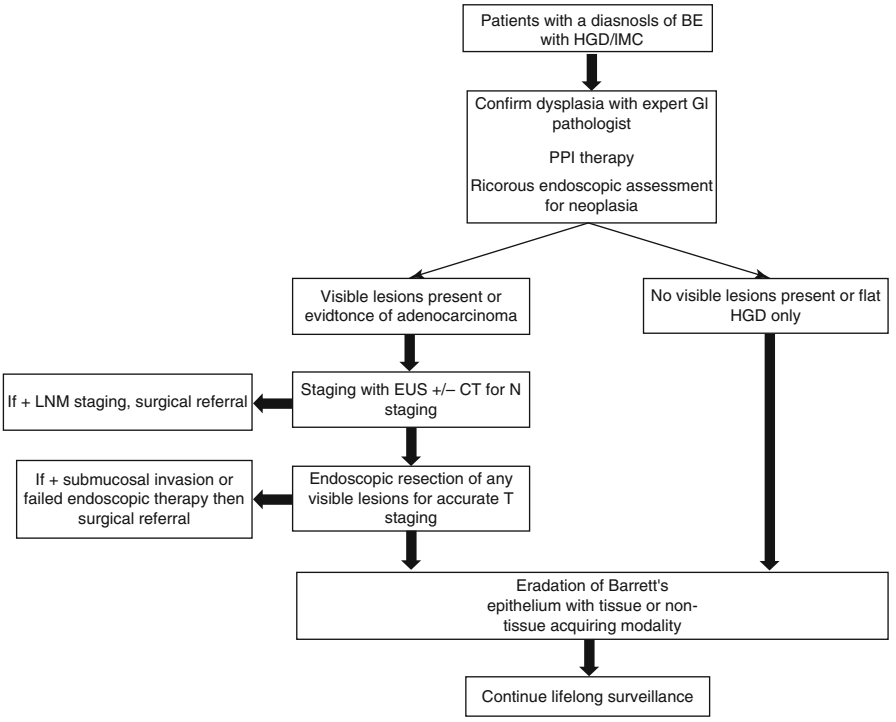

Fig. 22.1 An algorithm reflecting current standard approach for patients with Barrett's associated neoplasia

A Personal View of the Data

My approach systematically begins with counseling patients on all options of therapy and confirming the diagnosis of dysplasia with our gastrointestinal pathologists. I treat patients with high dose proton pump inhibitors twice daily. I standardly begin with a thorough endoscopic evaluation followed by endoscopic therapy. I utilize advanced imaging modalities that include narrow band imaging and/or confocal laser endomicroscopy to enhance my endoscopic examination to improve my diagnostic yield for biopsies and resections. Treatment for patients with high-grade dysplasia first begins with focal endoscopic mucosal resection of any visible lesions. Then, I treat the remainder of Barrett's mucosa radiofrequency ablation. Long segments are first treated with circumferential RFA with the balloon device. I treat shorter segments and residual areas with focal RFA. After treatment is completed, I perform surveillance endoscopies with biopsies yearly. I prepare patients with the knowledge that endoscopic treatment may require multiple modalities, multiple sessions, and indefinite surveillance.

Recommendations

- The presence of dysplasia should be confirmed by a gastrointestinal pathologist. (Evidence quality moderate; weak recommendation)
- Endoscopic resection of mucosal irregularities in the setting of dysplasia in Barrett's esophagus should be performed for accurate T staging of neoplasia. (Evidence quality low; weak recommendation)
- Patients with Barrett's esophagus with high-grade dysplasia should be managed with endoscopic eradication therapy rather than surveillance. (Evidence quality moderate; weak recommendation)
- Esophagectomy should be reserved for patients with Barrett's associated neoplasia with submucosal invasion, lymph node metastasis, or failure of endoscopic therapy (Evidence quality high; strong recommendation)
- Esophagectomy should be performed at high volume centers. (Evidence quality moderate; weak recommendation)

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