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Date:
2020-11-10

Citation:
Badgery, H., Read, M., Winter, N. N., Taylor, A. C. F. & Hii, M. W. (2020). The role of esophagectomy in the management of Barrett's esophagus with high-grade dysplasia. Annals of the New York Academy of Sciences, 1481 (1), pp.72-89. https://doi.org/10.1111/nyas.14439.

Persistent Link:
https://hdl.handle.net/11343/276161

The role of esophagectomy in the management of Barrett's esophagus with high grade dysplasia

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Short title: Esophagectomy and Barrett's esophagus

Keywords: Barrett's esophagus; dysplasia; esophagectomy; esophageal adenocarcinoma, endoscopy

Abstract

Barrett's esophagus (BE) with high grade dysplasia (HGD) has previously been a routine indication for esophagectomy. Recent advances in endoscopic therapy have resulted in a shift away from surgery. Current international guidelines recommend endoscopic therapy for BE with HGD irrespective of recurrence or progression of dysplasia. Current guidelines do not address the ongoing role of esophagectomy as an adjunct

in the setting of failed endoscopic therapy. This review examines the role of esophagectomy as an adjunct to endoscopy in the management of patients with BE and high grade dysplasia, with a specific focus on patients with persistent, progressive, or recurrent disease, disease resistant to endoscopic therapy, in patients with concomitant esophageal pathology, and in those patients in whom lifelong surveillance may not be possible or desired.

Introduction

Barrett's esophagus (BE) is the major risk factor for and only known precursor to esophageal adenocarcinoma (EAC).[1, 2] BE is metaplasia of the lower esophagus that occurs in response to chronic esophageal injury secondary to gastroesophageal reflux disease (GERD). In a small proportion of patients with BE, EAC develops through a stepwise progression from non-dysplastic BE (NDBE) to BE with low-grade dysplasia (LGD) and then high-grade dysplasia and finally EAC.[3, 4] Despite modest improvements in overall outcomes, EAC remains a condition with a poor prognosis, with a 5-year overall survival between 13% and 20%.[2, 5-7] Its incidence has increased five-fold since the 1970s and continues to increase at a rate faster than any other solid malignancy in Western countries.[7-12] This rise in incidence is not completely understood but may be explained by changes in risk factor prevalence and lifestyle factors, including obesity and GERD.[13] Effective management of BE with HGD is of great importance in the prevention of EAC.

Historically, patients with BE and HGD were managed with esophagectomy.[14, 15] This was effective in completely removing Barrett's tissue but was associated with significant morbidity and risk of mortality. With the development of new endoscopic techniques, there has been a dramatic shift towards endoscopic eradication therapies (EET) as first-line treatment. Numerous current guidelines recommend endoscopic resection and ablative techniques as initial treatment for dysplastic BE and early EAC.[4, 16-22] This is supported by high level evidence with existing meta-analyses and a systematic review and randomized controlled trials (RCTs) on the efficacy of EET, but no RCTs directly comparing EET with surgery.[23-26] There remains a role for surgery in a small subset of these patients, with the decision for esophagectomy made on a case-by-case basis. Unfortunately, evidence supporting decision making, in particular precisely when a patient should transfer from endoscopic treatment to surgery, is not currently available.[27] This literature review aims to examine the indications and the role of esophagectomy for patients with BE and HGD in the era of EET.

Search strategy

A review of the literature was conducted using the PubMed, Ovid MEDLINE, Cochrane Library, and Scopus databases. Search terms included "Barrett's esophagus" and "surgery or esophagectomy" and "endoscopic or

endoscopy" and "high grade dysplasia". Bibliographies from relevant guidelines, systematic reviews, and meta-analyses were reviewed and clinical studies on the management and outcomes of BE with HGD were included in the review.

Definition

Barrett's esophagus is defined by the American College of Gastroenterologists (ACG) as a premalignant condition where normal stratified squamous epithelium is replaced by metaplastic columnar epithelium, specifically goblet cell metaplasia above the gastroesophageal junction (GEJ), which extends into the tubular esophagus.[4] International definitions vary according to the requirement for intestinal metaplasia (IM) on histology. IM is a histological diagnosis where columnar-lined epithelium demonstrates specialized intestinal characteristics, including the presence of goblet cells.[4 28, 29] The United Kingdom guidelines define BE as distal esophageal mucosa that has been replaced by metaplastic columnar-lined epithelium, endoscopically visible, greater than 1 cm from the GEJ, and confirmed on histology irrespective of the presence of IM.[16] In the United States, Australia, and continental Europe, the majority of guidelines stipulate that the presence of IM is required to make a diagnosis of BE.[30, 31]

Epidemiology

The reported incidence and prevalence of BE is variable.[32] Ronkainen *et al.* examined prevalence using a random population sample with a gastrointestinal questionnaire (*n* = 3000) and upper endoscopy on a subsample of this group (*n* = 1000). Histologically confirmed BE was found in 1.6% of patients; the prevalence of BE in patients with GERD was 2.3% and 1.2% in those without.[33] A large population-based study using the Northern Ireland Barrett's Esophagus Register, a large endoscopy database of 261,000 procedures over 13 years, found a similar prevalence. They also noted an increasing incidence from 1.8% between 1993 and 1997 to 3.5% between 2002 and 2005, with a higher incidence in men.[34] Given the high proportion of asymptomatic cases and need for endoscopy in diagnosis, much of the existing data is on selected populations and may not reflect the prevalence in the general population.[8] Caucasians are disproportionately affected by Barrett's in comparison with other ethnic groups.[35] Western data therefore may not be generalizable to non-Western populations.[2]

Endoscopic therapies

EET is the first-line treatment for BE with HGD. There are no randomized trials comparing EET with surgery.[4, 16-21] Guidelines from the American Society for Gastrointestinal Endoscopy (ASGE) recommend endoscopic therapy over surgery or surveillance for BE with HGD.[4, 24] EETs include resection techniques such as endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), with the addition of ablative techniques such as radiofrequency ablation (RFA), argon plasma coagulation (APC), and photodynamic therapy (PDT).[36] The goal of EET is to achieve complete eradication of dysplasia (CE-D) and intestinal metaplasia (CE-IM) and subsequent re-epithelialization of squamous epithelium.[37] The use of RFA is supported by two RCTs comparing intervention with surveillance; however there is no RCT data for any other therapeutic techniques.[23, 26] Improvements in endoscopy equipment such as the development of high-definition white light endoscopy, magnification, and narrow band imaging have improved the ability to detect and eradicate Barrett's-related neoplasia.[38]

The decrease in the rate of esophagectomy for BE with HGD is driven by the development and uptake of these new endoscopic techniques.[39] Shaheen *et al.* (2009) demonstrated high rates of CE-IM with RFA, with prior resection of nodules if required (90% in patients with LGD, 81% in patients with HGD).[23] This marked the beginning of a shift in the treatment paradigm toward endoscopic therapy. Prospective cohort studies have demonstrated endoscopic therapies to be safe and effective in the treatment of BE with HGD.[40, 41]

Disease progression

The risk of progression from NDBE to EAC is between 0.12% and 0.61% per annum.[32, 42-46] The lifetime risk of NDBE to EAC is 7% to 13%. The lifetime risk of NDBE to a combined endpoint of HGD or EAC is 17% to 22%.[47] There is a wide range of reported rates of progression of dysplastic BE in the literature. Progression from LGD to HGD/EAC is between 1.3% and 23.2% and progression from HGD to EAC is between 16% and 60% per annum.[23, 48-55] A recent pooled analysis found the rate from LGD to HGD/EAC and the rate from HGD to EAC to be 10.5% per annum and 28.6% per annum, respectively.[53]

Given the cumulative ongoing risk of EAC, developing strategies to predict progression of disease has clinical relevance and may assist in targeting therapy to ensure effective treatment of disease and minimize the morbidity associated with overtreatment. One example is a validated model developed by Sravanthi *et al.* using male sex, smoking, BE length, and presence of dysplasia to predict annual risk of progression after initial

diagnosis of non-dysplastic BE from a low risk category (0.21% per annum) to a high risk category (2.1% per annum).[56] A number of biomarkers are also being investigated and are showing promise as a tool to predict disease progression, however, none have been validated for clinical use.[16, 57] Length of non-dysplastic BE is associated with increasing risk of progression to HGD or EAC, with one study finding the mean BE length of those who developed HGD/EAC versus those who did not being 6.1cm and 3.5cm respectively.[58]

Current guidelines for the management of BE make recommendations depending on degree of dysplasia.[4, 59] British guidelines recommend individualizing surveillance for NDBE based on length and histopathological findings. For NDBE without IM and length less than 3 cm on 2 separate endoscopies, patients can be discharged from surveillance given the low rate of progression (0.05%/annum).[16] The ACG and British Society of Gastroenterology (BSG) guidelines recommend 3–5 yearly surveillance for NDBE with IM.[4, 16, 17] EET is the recommended treatment for BE with LGD and HGD.[4, 16]

It is important to note that there is a small but fairly consistent proportion of patients in whom BE progresses to higher grades of dysplasia despite or during endoscopic therapy. The AIM dysplasia trial reported that 4.2% of patients had progressive disease despite radiofrequency ablation.[23, 55] In a similar trial by Phoa *et al.* (2014), 1.5% of patients undergoing RFA progressed, requiring esophagectomy.[60] A recent meta-analysis demonstrated 1.7% of patients progress despite therapy, though this figure may be underestimated due to inter-observer variability and diagnostic heterogeneity.[24, 61] This subgroup may represent patients with a more aggressive biology or more aggressive BE subtype. Multifocal HGD, nodular or ulcerated Barrett's metaplasia, HGD on initial endoscopy, and length of metaplasia have all been associated with treatment failure.[40, 41, 62, 63] Similarly, the development of EAC can occur despite endoscopic therapy. The ability to identify patients with more aggressive disease early could improve treatment planning and determine who may ultimately require more aggressive surveillance, treatment, or esophagectomy. The development of improved risk stratification tools is important to better define the role of surgery and minimize the risk of the development of EAC during EET or during post-EET surveillance.

Recurrent and persistent disease

Local recurrence of IM and dysplasia is relatively common following successful EET but is usually amenable to further endoscopic treatment.[64] Pech *et al.* (2008) studied the long term results following EMR of neoplasia within Barrett's esophagus and found a 21.5% metachronous disease rate after resection.[65] This was over a mean follow-up period of 63 months, with the median period of recurrence after remission being 17 months.

This study highlights the key argument for the use of ablative therapies with resection in reducing the rate of metachronous neoplasia. A meta-analysis by Krishnamoorthi *et al.* demonstrated a 9.5% annual recurrence rate of intestinal metaplasia following CE-IM with RFA and EMR of visible lesions. Where reported, 97% of these recurrences were amenable to further endoscopic treatment, with the remaining undergoing surgery if medically fit enough. Not all studies in the meta-analysis reported on subsequent treatment.[66]

In a meta-analysis, Fuji-Lau *et al.* found a pooled rate of IM and dysplasia recurrence of 4.8% and 2% annually, respectively.[67] Gupta *et al.* reported a much higher rate of recurrence: 20% at 1 year and 33% at 2 years post complete eradication of IM.[64] Sawas *et al.* (2019) found 14% of patients with BE with HGD receiving EMR and RFA achieved CE-D only with persisting IM.[37] This group were almost 3 times more likely to have recurrence of dysplasia and even more likely to develop recurrent HGD/EAC.

There is variation in the reported rates of recurrence and persistence following ETT. This is partly explained by a lack of a universally accepted diagnostic definition of Barrett's metaplasia. In a prospective trial, Cotton *et al.* found a greater probability of recurrence of IM in the first year after eradication, whereas Sami *et al.* found a constant rate of recurrence following complete eradication.[68, 69] There is also a small cohort of patients who do not achieve CE-IM with EET. These patients have a higher rate of dysplasia recurrence as compared with those who do achieve CE-IM (5% versus 12%).[37] There are several reported cases where patients have died from metastatic EAC after endoscopic treatment, with 1/169 in one study and 1/132 in another.[70-73] The overall rate of recurrent BE with dysplasia is 5.2/100 life years and the rate of recurrent non-dysplastic BE is 10.8/100 life years.[69] It is likely that patients with recurrent disease have a different biological subtype and more aggressive disease. In these patients, management strategies should be revisited and may require escalation of EET or consideration of surgery.[74] Our current understanding of the nature of Barrett's subtypes and how to identify these is inadequate to inform guidelines.

Surgery in Barrett's esophagus

In past decades, esophagectomy has been the mainstay of treatment for BE with HGD. This was underpinned by high rates of progression from HGD to EAC and a historically high incidence of occult invasive carcinoma (41%) found in esophagectomy specimens where index biopsy demonstrated BE with HGD.[75-77] Modern improved endoscopic diagnostic techniques have reduced the risk of occult carcinoma, with a more recent study finding a rate of 12.7%.[78, 79] The alternative approach to surgery was frequent surveillance endoscopy

with biopsy to monitor for progression of disease in order to avoid the morbidity and mortality associated with surgery.[76, 80]

Patients undergoing EET for BE with dysplasia, however, still require frequent and usually lifelong surveillance with biopsies to closely monitor disease.[4, 16, 17] With EET, surgery for BE with HGD has become far less common, with the rate of RFA now far exceeding the rate of esophagectomy.[39] A retrospective analysis using the National Inpatient Sample database in the United States found the rate of esophagectomy for BE cases was 3.2% in 2014 (3325 operations for 103,810 BE cases), which is decreased from 6% of cases in 2005 (3631 operations for 60,455 BE cases). Over this same period, the number of RFA procedures have increased from approximately 1000 to 30,000 per year and cryoablation had increased from 1550 procedures in 2007 to 2485 procedures in 2014.[39] The move from surgery to EET is supported by recent literature; however, long-term risk of progression and recurrence post EET, the malignant risk of buried Barrett's, and the safety of esophagectomy post EET remain untested.

The mortality and morbidity of esophagectomy has improved. Recent international data demonstrated an operative mortality of 2.6%. The vast majority of these cases were for squamous cell carcinoma (SCC) or EAC and were often higher risk patients, many being nutritionally deconditioned and post neoadjuvant chemotherapy and radiotherapy.[81] This data cannot be generalized to patients undergoing esophagectomy for BE who tend to be younger and fitter and where there is no requirement for neoadjuvant therapy.[82] A meta-analysis examining outcomes of esophagectomy and EET for BE with HGD and early EAC demonstrated a major adverse event rate and procedural mortality in esophagectomy of 28.3% and 1.2%, respectively; the rates for EET were 14.3% and 0.2%, respectively.[25] Major adverse events for EET include stricture formation, bleeding, and perforation as well as severe noncardiac chest pain. By comparison, major adverse events in esophagectomy include anastomotic breakdown, bleeding, and stenosis.[25] Major surgical complications often require prolonged hospitalization and, in certain cases, reoperation.

While esophagectomy can negate the need for ongoing therapy, complications of esophagectomy can require repeat endoscopic intervention. One study demonstrated anastomotic strictures developing in 25% of patients, requiring a median of 2 dilations. Refractory strictures are rare.[83] Anastomotic leaks are another significant complication that require endoscopy for diagnosis and characterization and can be managed endoscopically with stents, jejunal feeding tubes, and endoscopic clips.[84] The existing data on the endoscopic management of esophagectomy complications concerns cancer patients and is not necessarily generalizable to

the Barrett's population. The need for endoscopy for complications of esophagectomy is not uncommon; however, this is generally required in the short term during the post-operative period and does not require lifelong repeat intervention.[84]

A very high chance of immediate cure is the major benefit of esophagectomy. Dysplasia and early cancer can be eliminated in a single procedure. In a small trial of 23 patients, esophagectomy had a high rate of cure for submucosal tumors even in the presence of nodal disease (88% 5-year survival without nodal involvement, 67% 5-year survival with nodal involvement).[85] Nodal status cannot be determined with EET and this has implications, with unexpected mucosal or submucosal EAC following EET.[85, 86] In a major worldwide data series, 5-year survival of esophagectomy for T1 tumours was 75–80% and survival of HGD was 90%. The reported mortality rate, however, was not disease specific.[87] A large series of patients with HGD treated by esophagectomy demonstrated a higher survival rate than a matched general population sample after 4 years.[88] Similar rates of cure were demonstrated in smaller retrospective studies.[85, 89] These figures demonstrate a high rate of cure with excellent survival outcomes for BE with HGD and early EAC.

Current guidelines do not address the precise role of esophagectomy as an adjunct to or following failed endoscopic therapy. BSG, ACG, and the American Gastroenterological Association guidelines suggest BE recurrence should be managed as it was prior to initial therapy.[4, 16, 22] There are theoretical concerns with this approach. The cause of persistent or recurrent disease is not well understood and some of these cases may represent a subset of disease with more aggressive biology. In cases of multiple recurrences of BE, particularly with HGD, consideration of more definitive therapy or aggressive surveillance may be indicated, as with cases of disease progression despite EET. Luckett *et al.* identified a number of factors associated with failure of RFA (Table 1).[90] With RFA, 43% of patients failed to achieve CE-IM and 23.4% of patients failed to achieve CE-D, and 15.7% of patients were lost to follow-up and did not have post-treatment biopsies. The length of Barrett's segment (greater than 5 cm) and number of RFA sessions (more than three) were significant predictors.[90] GERD, smoking, and male sex were also associated with incomplete CE-IM and CE-D; however, this was not significant. The association between more treatment sessions and failure of eradication may be explained by a more aggressive or invasive phenotype of disease.

Indications for esophagectomy

While there are no absolute indications for esophagectomy for BE with HGD, there are a number of relative indications supported by varying levels of evidence. These can be divided into disease-related, procedure-related, patient-related, and institutional-related factors, as summarized in Table 2.

Disease-related factors

There is a strong association between length of BE (>8cm), multifocal dysplasia, and diffusely nodular BE with failure of endoscopic treatment.[86, 91] In the setting of multifocal HGD and nodularity, which is associated with unrecognized invasive EAC,[62, 92, 93] esophagectomy may still be appropriate.[27, 62, 94] In addition, failure of EET, as demonstrated by either recurrent disease, persistent disease, or disease progression, constitutes a relative indication for esophagectomy.[62, 86] However, although failure of EET is considered to be a relative indication, there is a lack of consensus within the literature regarding what constitutes 'failure of EET'. Consequently, the number of endoscopic procedures permitted without achieving CE-IM or CE-D differs widely in the literature. Shaheen *et al.* (2009) defined failed endoscopy as four procedures whereas Phoa *et al.* (2014) allowed five procedures after which point esophagectomy was considered.[23, 60] Zehetner *et al.* had no restrictions, with a range of one to eight sessions and a median of three sessions of EMR/RFA before achieving remission.[95]

Procedure-related factors

Complications relating to and hindering EET present another relative indication for surgery. Esophageal strictures can preclude endoscopic therapy if they cannot be dilated or if an endoscope cannot be passed. This limits the therapy at the site of stricturing as well as surveillance of the esophagus distal to this. Inability to resect within a stricture or the inability to lift mucosa should prompt consideration of surgery. The treatment of any stricture that may develop also increases the risk of esophageal perforation and further dissemination of disease.[96] The stricture rate is highest following PDT (18.5% of patients).[97] PDT is now rarely performed due to concerns regarding cost and complication rate.[98] RFA has a much lower rate (5.6%), with a higher rate when performed with EMR (10–13%).[99]

Importantly, the risk of the development of stricture secondary to EET is not an indication for surgery. Strictures can usually be addressed with endoscopic dilation. Rather, the development of strictures by any means can complicate further EET, making it technically challenging. In these situations, consideration of esophagectomy may be appropriate.

Iatrogenic endoscopic perforations also represent a relative contraindication to repeat endoscopic treatment. In this setting, esophagectomy may be warranted, as it deals with both the perforation and stricture, negating the need for ongoing surveillance and endoscopic treatment.

Patient-related factors

Concurrent esophageal disease should also prompt consideration of esophagectomy. In patients with significant esophageal disease such as severe achalasia or recalcitrant stricture, persistence with endoscopic therapy and organ preservation may not be in the best interests of the patient.[27] BE following treatment for achalasia is common. One study found 8.4% of patients with achalasia developing BE following treatment. In such cases, BE usually develops secondary to chronic GERD following myotomy and pneumatic dilatation.[100] These patients also have an increased risk of malignant transformation including squamous dysplasia and SCC due to esophageal stasis and post-treatment GERD.[101]

Quality of life implications should also be considered. Following EET, fear of recurrence has a negative impact on quality of life and this associated anxiety may not be acceptable to certain patients.[102] Certain patients, in particular young patients, may opt for definitive surgical management over lifelong surveillance.[27, 82, 95] Current guidelines suggest endoscopy every 3 months for the first year following clearance, every 6 months for the second year, and annually thereafter.[4] Rigid adherence to surveillance is vital, with the annual recurrence rate of dysplastic BE and HGD/EAC being 2% and 1.2%, respectively.[66] One study found 13% of patients treated with EET failed to attend follow-up appointments.[103] Patients in regional settings with poorer access to centers with specialized endoscopy units may have difficulty in attending and adhering to follow-up protocols. These factors should all be discussed with the patient; the patient's preference must also be taken into account.

Institution-related factors

Access to centers adequately equipped to manage BE endoscopically is important. Effective EET requires specialist training of endoscopists.[104, 105] There is also a requirement for rigorous lifelong surveillance that must be closely adhered to. Surveillance and therapy should be performed by specialist endoscopists at tertiary centers with the correct equipment.[16] Lack of access to such services constitutes another relative indication for surgery. While surgery also requires access to specialist centers, it does not necessitate ongoing repeat procedures, making patient access less prohibitive.

Esophagectomy following EET

Numerous episodes of prior EET may impact the outcome of esophagectomy.[62] Surgery following EET is likely to be more technically challenging due to peri-esophageal inflammation and scarring. A small case series (*n* = 15) demonstrated a morbidity and mortality of 40% and 7%, respectively, in patients undergoing esophagectomy following endotherapy[86]. This rate was higher than that reported in similar papers examining esophagectomy for HGD and early EAC without prior EET. Increased mediastinal fibrosis and plane obliteration was encountered, particularly in patients with longer segments of BE and serial ablations.[86] In light of this, early identification of endoscopic therapy–resistant disease and early consideration of surgery in select cases may be an important step in reducing the potential morbidity of esophagectomy.

Quality of life following surgery

In patients who undergo esophagectomy for dysplasia or early EAC, post-operative quality of life and long term functional outcomes remain positive.[106] Moraca *et al.*, examining health-related quality of life (HRQoL) post esophagectomy for HGD, found better HRQoL scores than a matched general population sample.[107] Sanghera *et al.* found in a review that most patients returned to their preoperative baseline approximately 9 to 12 months post esophagectomy.[108] Rosmolen *et al.* performed a prospective study comparing impact on quality of life following surgery versus endoscopic management in patients with BE and HGD. The impact on HRQoL was less in the endotherapy group; however, they suffered a degree of psychological stress surrounding the prospect of disease recurrence.[102]

Comparisons of EET and esophagectomy

There are 11 published reports that compare EET with esophagectomy in BE with HGD and early adenocarcinoma. These are summarized in Table 3. A Cochrane review initially conducted in 2008 and subsequently updated in 2012 found 13 published comparative studies, although there have been no published randomized controlled trials.[109, 110] Two papers from the Cochrane review were not included as they dealt only with EAC and not HGD.[111, 112] Patients treated surgically in these trials have generally failed endoscopic treatment due to recurrent or extensive disease and therefore may have more aggressive or treatment-resistant disease as compared with those that succeeded endoscopic therapy. Conversely, patients with fewer comorbidities and less extensive disease are more commonly managed endoscopically. In a meta-analysis, Wu *et al.* found a shorter mean BE length in endoscopically treated patients as compared with surgical patients. Additionally, the cardiac and pulmonary comorbidity rate was higher in the endoscopic group.[25] A number of outcomes have been examined in comparing EET with surgery, including efficacy,

mortality and morbidity, quality of life implications, cost, and survival. While the outcomes of EET are generally favourable, there are situations where EET is less appropriate.[25]

Zehetner *et al.* performed a retrospective study comparing endoscopic therapy with esophagectomy for HGD and intramucosal EAC. The rate of intramucosal cancer was higher in the surgery group. Of the 22 patients treated endoscopically, 2 ultimately required esophagectomy for recurrent HGD and 5 progressed to cancer prior to completion of ablation. Of the latter, 1 patient had developed submucosal cancer, the other 4 being mucosal. The development of a submucosal cancer is concerning as it represents a known curable disease progressing to a potentially incurable disease due to inadequate treatment. In the endotherapy group, 69% of patients achieved eradication of intestinal metaplasia. The long-term history of BE patients treated endoscopically is not known, with no long-term studies extending beyond 3–5 years.[55, 69, 95] Following remission through EET, there is an ongoing chance of late recurrence. Esophagectomy can effectively eradicate BE with HGD as demonstrated by several retrospective comparative studies.[103, 111-114] While more effective in eradicating BE, esophagectomy has a higher complication rate and mortality rate and this must be balanced against the treatment failure rate of EET.[103, 113, 115]

The shift away from esophagectomy is demonstrated by O'Farrell *et al.* in a single center study examining the proportion of BE with HGD and early EAC treated surgically versus endoscopically at different periods..[116] The existing studies comparing EET with esophagectomy demonstrated that endoscopic therapy is effective, with marginally lower cure rates and lower morbidity; however, these studies need to be interpreted with caution as they have significant limitations including selection biases and heterogeneity. All quantitative studies were retrospective, with inherent selection biases and noncomparable cohorts. In older studies, EET was generally offered to patients thought unfit for surgery based on frailty and age, though this is less of a consideration in more recent literature.[103, 110] There is also considerable variation among both surgical and endoscopic techniques, potentially impacting study outcomes. Furthermore, diagnostic uncertainty and a lack of definition consensus and inter-observer variability.

Cost

Esophagectomy in the treatment of dysplastic BE is cost effective.[117] Literature on the cost of surgery and endotherapy is summarized in Table 4. While Pohl *et al.* found endoscopic therapy to be more cost effective than surgery in a decision analysis model ($17,000 USD for endoscopic therapy versus $28,000 USD for surgery), this did not take into account long-term costs associated with repeat therapy and screening beyond 5

years. Surgery became more cost effective if long-term impact on quality of life was negligible and operative mortality rate did not exceed 1%[118] A similar finding was made by Chu *et al.*, where surgery was more cost-effective, provided a patient considered their quality of life post-surgery to be equal or improved than with endotherapy and risk of recurrence. Endotherapy was otherwise more cost effective per quality adjusted life year.[119]

Shembre *et al.* found higher initial costs for surgery but suggest it is more cost effective long term as those treated surgically are unlikely to generate further costs.[103] Hur *et al.* compared surgery with photodynamic therapy (PDT) and came to a similar conclusion.[120] Lifelong surveillance requirements present an ongoing cost that should be considered. There is considerable variation in cost among different endoscopic treatment techniques; this remains beyond the scope of this review.

Discussion

The management of BE with HGD has evolved, with almost all patients now being candidates for EET. The management of BE with HGD can, however, be complex and requires a nuanced approach taking into account patient expectations, comorbidities, and concomitant esophageal disease, clinical experience, prior treatments, and disease extent. This review has sought to explore the role of surgery for BE with HGD in the contemporary setting. There are a number of knowledge gaps regarding the use of EET for BE with HGD. These include the management of persistent disease following EET, early recurrence, and multi-recurrent disease, as well as the cost and quality of life implications of long-term EET. In these situations, esophagectomy should be considered on a case-by-case basis.

The published data supporting EET for BE with HGD demonstrates high rates of eradication of IM and dysplasia.[24] There is an important subgroup of patients with persistent disease despite treatment. Persistent BE or dysplasia may be under-recognized in the form of buried glands and potentially under-reported due to biopsy sampling error. Persistent IM after dysplasia eradication is significant as it is known to carry a higher risk of EAC.[37] While guidelines recommend repeat EET in the event of treatment failure, there is no agreement on how many attempts should be undertaken before considering surgery. Some existing studies have used arbitrary thresholds from three to six attempts, while others have had no restrictions.[23, 25, 95, 121] While having a defined number of sessions as a treatment cut-off may not be possible, using known factors associated with treatment failure should be incorporated to better guide ongoing treatment decisions. Given the association with poorer outcome of esophagectomy after extensive EET, persistence with endoscopic therapy may not be

advisable if success seems less unlikely.[86] In circumstances where success is less likely, earlier consideration of esophagectomy may be advisable to improve surgical outcomes.[62]

Patients with multi-recurrent disease following EET are another important subgroup. Review of the existing literature on this is difficult due to a lack of an accepted definition of persistent versus recurrent IM or dysplasia following EET. While most incidences of recurrent disease are amenable to further endoscopic therapy, the long-term implications of recurrent disease have not been reported, with no existing studies extending beyond five years.[37, 64, 66, 69] Given that the long-term risk of recurrence is lifelong, endoscopic follow-up is necessary.[64, 121] Current guidelines suggest persistence with endoscopic therapy and surveillance in cases of recurrent IM. Recurrent disease, in particular rapid or multi-recurrence, may be an indication of more aggressive disease. It may also be secondary to underlying patient factors such as poor compliance with risk factor modification and surveillance, and the presence of hiatus herniae and refractory GERD. Until additional information is presented regarding the natural history of these cases, these situations are likely to represent an alternative to routine eradication, requiring an alternative treatment pathway, and consideration of surgery should be given on a case-by-case basis.

Progression of dysplasia despite EET may also be a marker of a more aggressive phenotype of disease analogous to EAC that fails or progresses during neoadjuvant treatment. This subgroup should not be generalized to the broader BE population and may require more aggressive treatment. The AIM dysplasia trial demonstrated a small but important group of patients who had progression of disease despite endoscopic ablation (4%), with one patient developing intramucosal EAC despite treatment; the management of this was not reported.[23] Pech *et al.* (2008) reported that 3.7% of patients required surgery after failure of EET due to technical challenges secondary to iatrogenic scarring, unexpected submucosal cancer, and inability to achieve remission after multiple sessions due to poor healing post EMR.[65] Other studies on EET also have subgroups who develop progression of disease or who are found to have invasive carcinoma on EMR specimen but dysplasia on initial biopsy.[122] Clearer guidelines on the management of progressive disease and failed treatment are needed.

The cost and quality of life implications of BE treatment are significant. The impact on quality of life of BE therapy includes the anxiety surrounding fear of recurrence and malignant transformation in EET-treated patients. The rigorous and necessary screening requirements and follow-up treatment sessions require a high level of patient compliance and will not suit all patients, in particular young patients in whom lifelong

surveillance may not be acceptable or those in remote settings with poor access to an experienced tertiary center. While esophagectomy should also be performed at specialist centers, the important distinction is that surgery does not require ongoing repeat treatment and surveillance. Patients undergoing EET have a lesser impact on quality of life initially over esophagectomy. Much of the data on esophagectomy outcomes focus on invasive esophageal malignancy. Caution must be exercised when generalizing this data to patients with BE as they likely represent a healthier and less deconditioned cohort with lower clinical urgency, allowing for better preoperative optimization. While the initial cost of esophagectomy is substantial, it is unlikely to generate further costs in ongoing surveillance. In contrast, EET requires long-term follow-up with multiple repeat procedures leading to a high cumulative cost. While less relevant to older patients, this becomes a significant factor for young patients in whom lifelong surveillance is required. The cost and quality of life implications in surgery and EET are complex and should be balanced between long and short term implications.

The comparative literature on EET and esophagectomy carries a number of biases. The literature is predominantly retrospective. The endoscopic features of the BE cases are generally not well reported in the literature but it seems likely that patients selected for surgery will have features that may complicate EET, such as strictures, nodularity, and concurrent esophageal disease. Patients with suspected invasive disease were also more likely to undergo surgery over EET.[123] Significant differences in age and medical comorbidities as well as difference in Barrett's length between surgical and endoscopic cohorts is also likely to have influenced results.[25]

The majority of patients with BE with HGD should be offered EET, and this is well supported in the literature. However, there also remains a poorly defined group of patients for whom surgery should be considered. Unfortunately, the indications for surgery are difficult to precisely document with the existing literature base. The decision-making process is complex and, ultimately, the patient and clinician must be well informed on the relative risks and benefits of each approach in order to tailor the treatment decision accordingly. Multidisciplinary team discussion is appropriate and recommended to facilitate discussion and determination of appropriate therapy. The failure to eradicate BE with HGD with EET should prompt consideration of surgery. Progressive and multi-recurrent disease presents an ongoing concern; these cases may represent more aggressive biology and to delay more aggressive or definitive treatment may result in missing a therapeutic window where potentially curable disease becomes incurable. The development of improved biomarkers of disease progression and a better understanding of the natural history of the disease will improve our ability to predict progression and tailor treatment accordingly. Esophageal factors complicating endoscopic therapy may also indicate the need for surgical resection. Failure to consider these factors may lead to treatment-related complications, such as perforation, or treatment failure. Other factors associated with EET failure, including BE

segment length >8cm, nodularity, number of RFA sessions, and degree of dysplasia, should also be used to better guide treatment decisions and determine who might need esophagectomy earlier versus those in whom aggressive pursuit of EET is justified.[62, 86] Extensive high-grade dysplasia with concurrent disease along with patient preference and access issues are all relative indications for a patient to undergo surgery without first trialling EET. An improved ability to stratify risk and predict patients who are likely to fail EET is important and will help guide decision making, avoiding overtreatment and identifying those who may benefit most from surgery. Surgery should not be viewed as an alternate strategy to EET but rather a complementary therapy and should be considered where appropriate following discussion between the patient and treating team.

Conclusion

EET is the mainstay of management for patients with BE and HGD; however, there remains an ongoing role for surgery in selected cases or as an adjunct to unsuccessful EET. There are various relative indications that should prompt consideration of surgery. The decision for surgery is currently made on a case-by-case basis, with indications not well elucidated in the literature. Further data is required to better define the role of surgery and expand on existing treatment algorithms in the modern era of EET. Where appropriate, esophagectomy in the management of BE with HGD is cost effective, safe, durable, and efficacious, with an acceptable side-effect profile and impact on quality of life.

Acknowledgements

M.R. is recipient of the senior lecturer fellowship from the Royal Australasian College of Surgeons.

Author contributions

H.B. wrote the manuscript. M.H. provided supervision and guidance throughout the writing and research process and helped in structuring and writing drafts. M.R., N.W., A.T., and M.H. assisted in editing and contributed to the final drafting of the review as well as providing expert opinion.

Competing interests

The authors declare no competing interests.

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Table 1. Predictors of failure of CE-IM and CE-D in RFA patients[90]

Patient characteristics	CE-IM rate (%)	CE-IM failure rate (%)	CE-D rate (%)	CE-D failure rate (%)
Overall	57.0	43.0	76.6	23.4
HGD	39.3	43.5	36.6	56.0
LGD	60.7	56.5	63.4	44.0
Length ≤5cm	72.1	43.4	63.4	48.0
Length >5cm	27.9	56.6	36.6	52.0
≤3 RFA sessions	67.2	45.7	63.4	40.0
>3 RFA sessions	32.8	54.3	36.6	60.0

Table 2. Relative indications for consideration of esophagectomy for BE with HGD

Disease-related	Procedure-related	Patient-related	Institutional-related
Long segments of BE	Failure to eradicate despite repeat treatment	Existing additional esophageal pathology (e.g., end-stage achalasia)	Access to appropriately trained endoscopists
Presence of multinodular dysplasia	Inability to pass esophageal stricture	Surveillance compliance post EET	Ability to perform lifelong surveillance
Inability to eradicate IM or dysplasia endoscopically	Inability to resect within stricture	Anxiety surrounding recurrence	
Multiple recurrences of disease (IM or dysplasia)	Inability to lift mucosa following previous intervention	Patient preference	
Rapid recurrence of disease	Previous or concurrent endoscopic perforation		
Progression to higher stage disease			

Table 3. Summary of comparative studies on surgery and endotherapy for BE with HGD +/- early EAC.

Study	Study design	Modalities (patients)	Disease	Mean follow-up time (EET/surgery, months ± SE)	Characteristics (EET/surgery)	Significant outcomes (EET/surgery)
Pacifico (2003)[113]	Retrospective single-center	EMR/PDT (24); surgery (64)	BE with HGD, intramucosal EAC	12 ± 2/ 19 ± 3	Age[a]: 68/67 Length[b]: 5.6/6.5 CCR: 42%/31% PCR: 42%/19%	Stricture rate: 16%/6% Procedure-related mortality: 0%/1.5% Cancer-free follow-up: 83%/100% EET failure: 17%
Prasad (2007)[115]	Retrospective single-center	PDT (129); surgery (70)	BE with HGD	59 ± 2.7/ 61 ± 5.8	Age[a]: 64.5/60.3 Length[b]: 5.0/7.0 CCR: 30%/14% PCR: 12%/7% ASA 3+: 14%/24%	Overall survival: 91%/91.5% Procedure-related mortality: 0%/1.4% PDT failure: 25% EAC post EET: 6.2%
Reed (2005)[114]	Retrospective single-center	EMR/PDT (47); surgery (49)	BE with HGD	NR/56[c]	Age[a]: 70.0/59.0	5-year survival: NR/83%; 10-year survival: NR/64% Disease-specific survival: NR/94% EET failure: 3 deaths (recurrent disease)

						T1 + EAC surgical specimen histology: 37%
Schembre (2008)[103]	Retrospective single-center	PDT, EMR, APC, combination (62); surgery (32)	BE with HGD or IMC	20/48[c]	Age[a]: 70.0/64.0[c] Length[b]: 5.1/7.2 ASA[d]: 2.6/2.5	Overall 4-year survival: 89%/93% Persistent dysplasia: 13%/3% Progression to EAC: 6%/0% T1 + EAC surgical specimen histology: 25% Operation mortality: 2%/0% Major complications: 8%/13% Hospital charges: $40,079/$66,060
Yachimski (2008)[124]	Retrospective single-center	APC, PDT, PDT/EMR (137); surgery (82)	BE with HGD or EAC	NR	Age[a]: 64.5/60.3 Length[b]: 5.0/7.0 CCR: 30%/14% PCR: 12%/7%	Factors associated with esophagectomy: age (<60), initial consult by surgeon (versus gastroenterologist) (OR = 35.1), Cancer stage T1sm or greater (OR = 16)
O'Farrell (2013)[125]	Retrospective single-center	EMR + RFA (25); surgery (40)	BE with HGD, IMC + T1sm	NR	Age[a]: 67.0/65.0 Length[b]:	Proportion surgery 2000-2006: 96% Proportion

					5.4/5.5 ASA 3+: 20%/10%	surgery 2007-2011: 55% Morbidity: 35%/4%
Rosmolen (2010)[126]	Retrospective cross-sectional study	Endotherapy (66); surgery (29)	BE with HGD or early EAC	12–60 months post treatment		Endotherapy group reported greater fear of recurrence. Surgery group reported eating problems + reflux symptoms
Rosmolen (2017)[102]	Prospective cohort QoL study	EMR/RFA (42); surveillance (44); surgery (21); advanced surgery (28)	BE, BE with dysplasia, early EAC, ≥T1N1	Questionnaire 2 + 6 months post Rx	Age[a]: 62.7/64.8 Length[b]: NR	Endotherapy group reported greater fear of recurrence Surgery group reported worse QoL on physical + mental scale of SF-36 + EORTC-QLQ-C30
Schembre (2010)[127]	Retrospective single-center QoL study	EMR, PDT, APC, combination (27); surgery (13)	BE with HGD or IMC	NR	Age[a]: 70.0/63.0[†] Length[b]: 5/7 ASA[d]: 2.6/2.5	Similar QoL impact of endotherapy + surgery based on SF-36 + GIQLI. No significant difference found Negative QoL impact greater on younger surgical patients
Thomas (2005)[128]	Retrospective review of BE with HGD Mx	APC (5); surveillance (2); surgery (8)	BE with HGD	21/60	Age[a]: 70.0/58.0 Length[b]: 6.0/7.6	Overall survival: NR/62.5% at 18.5 months

Zehetner (2011)[95]	Retrospective single-center	EMR/RFA (40); surgery (61)	BE with HGD ± IMC	34/17[c]	Age[a]: 66.0/68.0[c] Length[b]: 3.0/4.0 CCR: 28%/36% PCR: 43%/33%	Morbidity: 0%/39% 3-year survival: 94%/94% EET failure: 3 patients (2 HGD, 1 EAC)

[a]Years

[b]Mean length (cm)

[c]Median value

[d]Average score

PCR, pulmonary comorbidity rate; CCR, cardiac comorbidity rate; NR, not reported; SF-36, short form (36) health survey; GIQLI, gastrointestinal quality of life index; EORTC-QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; SE, standard error; ASA, American Society of Anesthesiologists; CCI, Charlson Comorbidity Index

Table 4. Cost and quality-adjusted life years (QALYs) of Barrett's esophagus (BE) treatments

Study	**Design (country)**	**Cohort**	**Treatment modalities**	**Outcomes (Cost/QALYs)**	**Comments**
Schembre (2008)[103]	Retrospective review from single institution	94 patients with BE and HGD or early EAC	Endotherapy, esophagectomy	Endotherapy: $40,079 USD Esophagectomy: $66,060 USD	QALYs not assessed
Boger (2010)[11]	Cost-utility analysis; Markov model (UK)	Hypothetical cohort of 100 patients age 64 with HGD in BE	Esophagectomy, RFA with surveillance, esophagectomy for recurrent/persistent EAC/HGD on surveillance	Endoscopy: £6,653/14.2 Esophagectomy: £8,555/13.8	Surveillance as per UK guidelines

Pohl (2009)[118]	Decision analysis (U.S.)	Base-case patient: 65M with early EAC	Esophagectomy, EMR with ablation, surveillance with esophagectomy for recurrence	Endoscopy: $17,408 USD/4.9 Esophagectomy: $27,830 USD/4.6	Study examines EAC (rather than dysplastic Barrett's)
Hu (2016)[129]	Decision analysis model (U.S.)	Base-case patient: 65M with HGD	Esophagectomy versus EMR-RFA + surveillance +/- esophagectomy	Endoscopy: $52,500 USD/11.5 Esophagectomy: $74,300 USD/11.4	20-year period
Inadomi (2009)[130]	Decision analysis model (U.S.)	Hypothetical cohort of patients aged 50 with BE with HGD, LGD, and no dysplasia	No surveillance, RFA + surveillance, APC with surveillance, PDT with surveillance, surveillance, esophagectomy	No surveillance: $1,859 USD/12.4 RFA with surveillance: $20,776 USD/15.7 APC with surveillance: $22,117 USD/15.6 PDT with surveillance: $34,580 USD/15.7 Surveillance: $48,354 USD/14.82 Esophagectomy: $58,973 USD/15.0	Figures shown for BE with HGD only
Hur (2003)[120]	Markov Model (U.S.)	Base-case patient: 55M with HGD	Surveillance, esophagectomy + surveillance, PDT + surveillance	Surveillance: $27,800 USD/10.0 Esophagectomy: $41,100 USD/9.4 PDT: $48,200 USD/11.6	