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## Barrett's esophagus: Review of natural history and comparative efficacy of endoscopic and surgical therapies

Kevin Kyung Ho Choi, Santosh Sanagapalli

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### Abstract

Barrett's esophagus (BE) is the precursor to esophageal adenocarcinoma (EAC). Progression to cancer typically occurs in a stepwise fashion through worsening dysplasia and ultimately, invasive neoplasia. Established EAC with deep involvement of the esophageal wall and/or metastatic disease is invariably associated with poor long-term survival rates. This guides the rationale of surveillance of Barrett's in an attempt to treat lesions at an earlier, and potentially curative stage. The last two decades have seen a paradigm shift in management of Barrett's with rapid expansion in the role of endoscopic eradication therapy (EET) for management of dysplastic and early neoplastic BE, and there have been substantial changes to international consensus guidelines for management of early BE based on evolving evidence. This review aims to assist the physician in the therapeutic decision-making process with patients by comprehensive review and summary of literature surrounding natural history of Barrett's by histological stage, and the effectiveness of interventions in attenuating the risk posed by its natural history. Key findings were as follows. Non-dysplastic Barrett's is associated with extremely low risk of progression, and interventions cannot be justified. The annual risk of cancer progression in low grade dysplasia is between 1%-3%; EET can be offered though evidence for its benefit remains confined to highly select settings. High-grade dysplasia progresses to cancer in 5%-10% per year; EET is similarly effective to and less morbid than surgery and should be routinely performed for this indication. Risk of nodal metastases in intramucosal cancer is 2%-4%, which is comparable to operative mortality rate, so EET is usually preferred. Submucosal cancer is associated with nodal metastases in 14%-41% hence surgery remains standard of care, except for select situations.

**Key Words:** Barrett's esophagus; Endoscopic eradication therapy; Dysplasia; Adenocarcinoma; Natural history; Radiofrequency ablation

**Core Tip:** Barrett's esophagus (BE) is an important premalignant condition. The last two decades have seen treatment paradigms increasingly shift towards endoscopic eradication therapy for dysplastic and early neoplastic cases, where it appears safe and effective. We herein provide a comprehensive review of the literature relating to Barrett's natural history and comparative efficacy of surveillance, endoscopic and surgical therapies for BE by histological stage.

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## INTRODUCTION

Barrett's esophagus (BE) is an acquired condition characterised by metaplastic change of esophageal mucosal cells in response to chronic gastro-esophageal reflux. While the very definition of BE is variable (and controversial), it is most commonly diagnosed in the presence of salmon-colored mucosa extending at least 1 cm proximal to the gastroesophageal junction, where there is histopathological confirmation of replacement of normal squamous epithelium by metaplastic intestinal-type columnar epithelium. Its clinical importance primarily relates to its established status as a precursor lesion to esophageal adenocarcinoma (EAC)[1]. Worldwide, esophageal cancer ranks seventh in incidence and sixth in overall mortality[2], and is subdivided into squamous cell carcinoma and adenocarcinoma. The incidence of EAC is rising in both Western and Eastern parts of the world[3,4], with EAC now becoming the dominant type of esophageal cancer in high-income, Western countries[3-7]. EAC is associated with high morbidity and mortality, and is commonly diagnosed late with metastatic disease[5,8].

On the other hand, it is clear that in the majority of cases, EAC arises within a segment of pre-existing BE[9]. BE is thought to progress to EAC in a stepwise fashion *via* the development of dysplasia and finally, neoplasia. Hence it is logical that surveillance of patients with established BE may prevent the poor outcomes associated with EAC by the detection of treatable premalignant or earlier stage localized malignant lesions, and this seems to have been borne out in some data[10]. Recent data from the United States show metastatic EAC at diagnosis has a 5-year survival rate of 4.3%, whereas local disease has a 40.3% 5-year survival[11]. This forms the rationale for Barrett's surveillance programs that are recommended by international societies[12-14]. Concomitant with increased surveillance of BE, recent decades have also seen significant advances in therapeutic options for premalignant Barrett's, with endoscopic therapies now having entered widespread use for premalignant BE and for some cases of early EAC. This has led to significant changes in international consensus recommendations for management of BE, though these are not always entirely in agreement with each other. Controversy in management of BE persists, primarily arising from persistent uncertainties regarding natural history and identification of dysplasia.

The purpose of this review therefore is to assist the treating physician in efficient decision making in patients with BE or early EAC by reviewing the current literature regarding natural history of BE, and comparing this to our current understanding of the risks and expected efficacy of current management options including surveillance, endoscopic therapy and surgery.

## LITERATURE

A comprehensive Medline search was performed using the following keywords and phrases: "Barrett's esophagus, non-dysplastic Barrett's esophagus/oesophagus, low grade dysplasia, high grade dysplasia, surveillance, esophageal cancer, Barrett's endoscopic therapy, endoscopic eradication therapy, radiofrequency ablation, endoscopic resection, esophagectomy, lymph node metastasis, adenocarcinoma, intramucosal adenocarcinoma, T1a esophageal/oesophageal adenocarcinoma, submucosa adenocarcinoma T1b esophageal/oesophageal adenocarcinoma, meta-analysis, systematic review". There was a focus on original and high-quality research. In addition, we manually reviewed reference lists of all citing references to ensure no relevant articles were excluded.

## STAGES OF BARRETT'S ESOPHAGUS AND NEOPLASIA

Since EAC is thought to arise in a stepwise histopathological progression from BE (Figure 1)[15], the optimal management strategy is primarily dependent on the degree of dysplastic and neoplastic stage. There is considerable variability in nomenclature, but for the purposes of this review the following classification will be used[16].

### Non-invasive neoplasia

Non-dysplastic BE: Intestinal metaplasia without histological features of dysplasia.

BE with low grade dysplasia (LGD): Intestinal metaplasia with histological features of low-grade dysplasia or intra-epithelial neoplasia.

BE with high grade dysplasia (HGD): Intestinal metaplasia with histological features of high-grade dysplasia or intra-epithelial neoplasia. HGD is synonymous with carcinoma in situ, Tis[17], non-invasive carcinoma, suspicion of invasive carcinoma, or defined by malignant cells confined by the basement membrane.

### Invasive neoplasia

Intramucosal EAC: Invasion of neoplastic cells beyond the basement membrane into the mucosa but not into the submucosa (T1a[17]).

Submucosal EAC: Invasion of neoplastic cells beyond the basement membrane into the submucosa (T1b[17]).

T2 EAC: Invasion beyond submucosa but confined to the muscularis propria[17].

## NATURAL HISTORY OF BARRETT'S ESOPHAGUS AND EARLY STAGE ESOPHAGEAL ADENOCARCINOMA

Consideration of natural history is essential when evaluating the utility of interventions for any condition. In BE, the most important and clinically relevant endpoint is development of adenocarcinoma, and will be the focus of review for natural history studies of premalignant BE. Where early stage adenocarcinoma has already developed within BE, the endpoint of interest is nodal metastases, since this is the major factor determining appropriateness of endoscopic or surgical therapy.

### Risk of adenocarcinoma

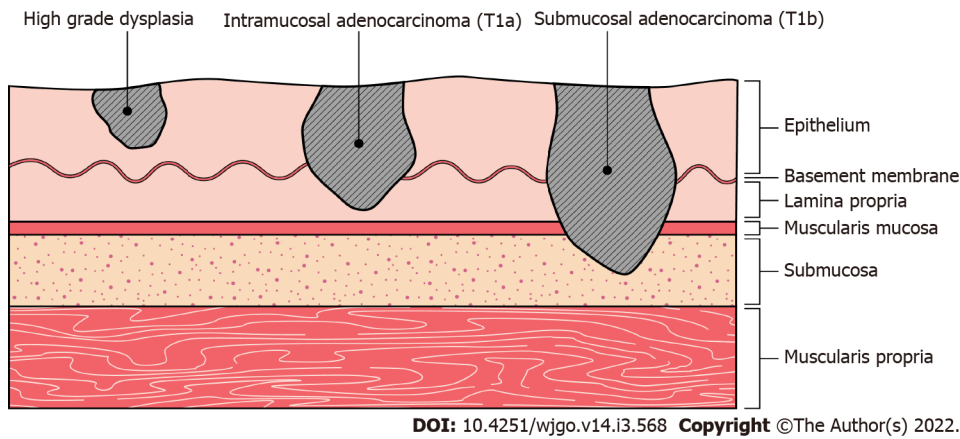
**Non-dysplastic Barrett's:** There is a large body of data examining the risk of cancer progression for non-dysplastic BE. Several meta analyses incorporating multiple retrospective case series have reported annual progression rates of non-dysplastic BE to cancer of between 0.33%–0.70%[18–41]. Within this range, Shaheen *et al*[18] showed an inverse relationship between study size and cancer risk whereby small studies tended report higher progression rates[18]. Meta-analyses reporting higher progression rates also tended to incorporate a significant minority of LGD cases that were not separated in analyses [20,21,23] (Supplementary Table 1).

Population-based studies have reported rates of progression at the lower end of the abovementioned range. De Jonge *et al*[29] showed from a registry in the Netherlands including more than 38000 subjects an annual progression rates of 0.39% after careful exclusion of prevalent HGD and EAC cases[29] and even lower rates have been found in other national databases[30,31]. The only prospective natural history study in patients with non-dysplastic BE followed 150 subjects over 5.5 years that led to 3 cases of EAC (annual progression rate 0.36%)[25]. Taken in sum, the annual risk of cancer in those with non-dysplastic BE is felt to be below 0.5%.

**Barrett's with low grade dysplasia:** There is marked heterogeneity in the reported rate of progression of LGD-BE to EAC. This is now thought to primarily relate to the significant variability in the classification of LGD by pathologists. Traditionally, the risk of progression of LGD was deemed low. Several large, multicenter series suggested that the annualized risk of progression to EAC was less than 1%[25–27,34,42]. However, due to concerns including non-centralized histopathology reading, marked interobserver variability in dysplasia diagnosis, short follow up duration and significant rates of regression of dysplasia in follow up, the possibility of overstaging of dysplasia in these studies was raised. Several population-based studies based on national registry data from the United States and Europe also reported similar rates of between 0.24% and 0.92%[29,31,33,43]. Such data is subject to the same limitations as cohort studies as they include patients from smaller centers where overdiagnosis of LGD is even more likely to occur.

Several studies have attempted to address the issue of overstaging of dysplasia and suggested that the true rate of progression to EAC may be higher. Curvers *et al*[24] had pathology specimens from 147 subjects with LGD re-examined by an expert panel who downstaged the diagnosis in 85%. Of the minority who were confirmed to have LGD by the expert panel, the annualized risk of progression to





**Figure 1** Progression from high grade dysplasia to intramucosal adenocarcinoma to submucosal adenocarcinoma in each respective layer.

EAC was 3.3%. This was significantly higher than in those who were downstaged to non-dysplastic BE where progression rate to EAC or HGD was only 0.49%, thus providing a convincing argument that inconsistency in pathological diagnosis was the major factor in variability in reported progression rates. Duits *et al*[37,44] similarly demonstrated that the majority of cases of LGD-BE diagnosed in community centers are downstaged by a centralized expert panel; but those who are confirmed dysplastic have a higher rate of progression than previously thought[37,44]. The control arm of the SURF trial, examining outcomes in LGD-BE, also found that when LGD was confirmed by an expert panel of experienced pathologists, the rate of progression to EAC was 2.9% *per annum*[45]. In contrast, a recent well-designed RCT with expert GI pathologists and central pathology review, showed that even after downstaging 26% of patients initially thought to have LGD, progression of 'true' LGD to EAC in those under surveillance was a low 2.4% at three years[46]. The authors identified nearly 1/3 of their initial diagnosis of LGD spontaneously regressed raising the issue of potential consensual misclassification of the diagnosis of LGD. Even in the presence of agreement between multiple expert pathologists k-values may still be suboptimal[37,47,48], thus not completely eliminating the issue of overdiagnosis in LGD.

Therefore, the risk of progression of LGD-BE depends upon the rigor by which it is diagnosed. There can be significant variability in diagnosis depending on local expertise and experience. It is clear that diagnosis in community centers can be unreliable, and when the diagnosis of LGD is made, biopsies should be repeated and examined by at least two expert gastrointestinal pathologists. If a conclusive diagnosis of LGD remains, then the annualized risk of progression to cancer may approximate 1%–3% (Supplementary Table 2).

**Barrett's with high grade dysplasia:** There is a paucity of high-quality literature describing true progression rates of HGD-BE to EAC. Only three small single center observational studies exist reporting annual incidence rates of cancer between 5% and 8.7%[49-51]. Two well-conducted meta-analyses primarily comprising the abovementioned studies reported identical weighted risks of cancer of 6.6% *per annum*. A single randomized controlled trial included in the meta-analyses followed 70 subjects with HGD-BE over the course of 3.3 years. 19 of these patients developed EAC giving an annual progression rate of 8.14%[52].

While not as significant of an issue as for LGD, pathological overstaging of dysplasia may also be a problem in HGD-BE[53]. Two additional studies suggested that when HGD-BE was characterized following consensus amongst more than one pathologist, the annual risk of progression was higher and between 19%–31.25%[32,42]. Regardless, the annual risk of cancer in HGD-BE is certainly high and is at least in the range of 5%–10% (Supplementary Table 3).

#### Rate of lymph node metastasis

Conceptually, lymph node metastasis is the major factor that precludes the curative potential of endoscopic therapy for early adenocarcinoma in BE. Lymph node metastasis is also an important outcome as it leads to higher mortality[54-59], tumor recurrence[57,60,61] and is an indication for systemic therapy[62,63]. Most data that assesses risk of lymph node metastases comes from retrospective studies with histopathological lymph node dissection samples from esophagectomy specimens, therefore is significantly limited by selection bias.

**Barrett's with high grade dysplasia:** HGD, that is, neoplasia confined to the mucosa that does not extend through the basement membrane confirmed by expert gastrointestinal pathologists, has a negligible lymph node metastasis rate[54,60,64-67]. This was confirmed by a systematic review in 2012 which compiled 524 subjects with HGD-BE showing a lymph node metastasis rate of 0%[68].



**Intramucosal adenocarcinoma:** There is a wide range in the reported rate of lymph node metastasis in intramucosal cancer, ranging between 0% and 9.5% [55-61,64,67-78]. However most of these studies arise from retrospective surgical series suffering from small sample sizes and selection bias [55-61,64,67,69-78]. Larger population database studies tend to suggest much lower rates of lymph node metastasis. A recent retrospective cohort study comprising 782 patients and using the National Cancer Database capturing 70% of all cancers in the United States, showed a relatively low lymph node metastasis rate of 3.6% for intramucosal adenocarcinoma [54]. The reliability of this study stems from including patients with clear staging and adequate lymph node sampling [54]. Another large United States database identified 3595 individuals with intramucosal adenocarcinoma who had undetected lymph node metastatic rate of 8.7% [74], though 16% of the cohort had squamous cell carcinoma which may tend to metastasize to lymph nodes earlier [79]. Further, a systematic review including 1350 patients with intramucosal adenocarcinoma identified 26 individuals with metastasis to surrounding lymph nodes. After prevalence rates were weighted for study sample size, a lymph node metastasis rate of 1.93% was reported.

It appears intramucosal adenocarcinoma has an approximate lymph node metastasis risk between 2%–4% (Table 1). Those with high risk features (invasion into the muscularis mucosae, poor differentiation, and lymphovascular invasion) may have greater risk of metastasis [61].

**Submucosal adenocarcinoma:** An even wider discrepancy exists in lymph node metastasis for submucosal adenocarcinoma ranging from 14% to 41% (Table 2) [55-61,64,67,69-78]. Such variation is explained by a number of factors. The number of lymph nodes resected during esophagectomy vary widely, and are often not reported; those with greater numbers of nodes excised tend to show higher metastasis rates [73].

Further, other factors may significantly impact rates of lymph node metastases in submucosal disease. Lymphovascular invasion, poor differentiation and size (2 cm) are prognostic factors known to increase the risk of lymph node metastasis [54,55,57,58,60,64,65,67,69,70,72,73,80]. A study by Sepesi *et al* [72] contained a cohort of submucosal adenocarcinoma patients with almost a third exhibiting poor differentiation and found a lymph node metastasis rate of 31% [72]. In contrast, a large retrospective study containing 14000 subjects identified a lymph node metastasis rate of 8.6% when tumors were smaller than 2 cm and well to moderately differentiated [64]. Even lower rates of 1.9% have been reported where invasion depth into the submucosa was shallow and no other poor prognostic features were present [81]. Several other studies identify depth of submucosal invasion as another independent risk factor for nodal metastasis in submucosal disease, but this is not a universal finding [56-58].

## MANAGEMENT STRATEGIES

### Surveillance

Surveillance of BE is recommended by all international societies for all patients who have a history of non-dysplastic BE, and is one of the strategies available for LGD-BE [12-14]. Surveillance involves dye-based [82] or virtual chromoendoscopy [83] in combination with white light endoscopy [13] using a systematic 4-quadrant biopsy protocol (Seattle protocol) [84]. The surveillance interval is determined by a risk appraisal based on the prior endoscopic and histological findings.

### Barrett's endoscopic eradication therapy

Barrett's endoscopic eradication therapy (EET) has become an established therapeutic modality for dysplastic and early neoplastic BE. EET is an umbrella term given to a multimodal therapeutic strategy whereby nodular components of the BE segment are endoscopically resected, with subsequent treatment of residual flat components of the segment with ablative therapies.

**Resection:** Resection is the first component to successful EET. It relies on a careful high-quality endoscopic examination with white light as well as an enhanced imaging modality (dye-based or virtual) for detection of nodular or irregular lesions. Resection is vital from a therapeutic standpoint but also assists in staging by providing depth of tumor invasion that cannot be ascertained from mucosal biopsies alone [85]. The most widely used resection technique in BE is endoscopic mucosal resection (EMR). EMR can be performed using the cap and snare technique or by multi-band mucosectomy [86, 87].

Endoscopic submucosal dissection (ESD) is an advanced resection technique that has theoretical advantages of allowing en bloc resection and thorough assessment of lateral and deep margins of the specimen. However, ESD is technically challenging, time consuming, has a steep learning curve, and is not as widely available. Further, it has not been clearly shown to be superior to EMR for neoplasia remission, recurrence or need for surgery in BE [88]. At present, it is usually reserved for large lesions with endoscopic evidence of submucosal invasion [89].

**Table 1 Efficacy of surgery for Barrett's esophagus with intramucosal adenocarcinoma**

Ref.	Type	n <sup>1</sup>	LNMrate	5-yr DFS or DSS	5-yr OS
Rice <i>et al</i> [97]	Retrospective	53	2%	-	77%
Liu <i>et al</i> [61]	Retrospective	53	-	100%	91%
Prasad <i>et al</i> [75]	Retrospective	46	8.6%	97%	95%
Pennathur <i>et al</i> [59]	Retrospective	29	7%	82%	73%
Wang <i>et al</i> [109]	Retrospective	60; T1a 32%; HGD 68%	-	-	88%
Sepesi <i>et al</i> [72]	Retrospective	25	0%	-	85%
Zehetner <i>et al</i> [96]	Retrospective	48	-	88%	94% (3 yr)
Hölscher <i>et al</i> [56]	Retrospective	70; SCC 29%	0%	-	87%
Leers <i>et al</i> [55]	Retrospective	75	1.3%	98%	82%
Pech <i>et al</i> [95]	Retrospective	38	-	100% (3.7 yr)	93%
Ngamruengphong <i>et al</i> [120]	Retrospective	671	-	-	76%
Lorenz <i>et al</i> [57]	Retrospective	42	8.7%	93.4%	91%
Newton <i>et al</i> [54]	Retrospective	303	3.6%	-	80%
Marino <i>et al</i> [121]	Retrospective	1317	-	-	79%
Semenkovich <i>et al</i> [74]	Retrospective	428; SCC 16%	8.7%	-	80%

<sup>1</sup>Pure T1a cohort unless otherwise stated.

DFS: Disease free survival; DSS: Disease specific survival; HGD: High grade dysplasia; LNM: Lymph node metastasis; OS: overall survival; SCC: Squamous cell carcinoma.

**Table 2 Efficacy of surgery for Barrett's esophagus with submucosal adenocarcinoma**

Ref.	Type	n	LNM rate	5-yr DFS	5-yr OS
Rice <i>et al</i> [97]	Retrospective	31	5%	-	60%
Liu <i>et al</i> [61]	Retrospective	37	-	60%	58%
Pennathur <i>et al</i> [59]	Retrospective	71	27%	62%	60%
Sepesi <i>et al</i> [72]	Retrospective	29	31%	-	60%
Hölscher <i>et al</i> [56]	Retrospective	101; SCC 35%	34%	-	66%
Leers <i>et al</i> [55]	Retrospective	51	22%	79%DSS	71%
Ngamruengphong <i>et al</i> [120]	Retrospective	523	-	-	64%
Lorenz <i>et al</i> [57]	Retrospective	168	20.6%	85%	74%
Schölvinck <i>et al</i> [78]	Retrospective	26	17% (n = 69 including EET group)	-	Median survival: 51 mo
Schwameis <i>et al</i> [76]	Retrospective	32	22%	-	84%
Newton <i>et al</i> [54]	Retrospective (NCDB)	512	23.4%	-	64.4%
Semenkovich <i>et al</i> [74]	Retrospective (NCDB)	1146; SCC 16%	14%	-	60%
Otaki <i>et al</i> [77]	Retrospective	68	14.7%	92%	89%

DSS: Disease specific survival; EET: Endoscopic eradication therapy; NCDB: National cancer database; DFS: Disease free survival; OS: Overall survival; SCC: Squamous cell carcinoma.

**Ablative therapy:** Ablation always follows resection other than in the scenario where all visible intestinal metaplasia has been endoscopically resected. It is typically applied to LGD-BE or flat HGD-BE. There are numerous modalities of ablative therapy, however the technique with the best efficacy, ease of use and favorable safety profile is radiofrequency ablation (RFA)[90]. RFA is applied using a

catheter with distal balloon or other attachment bringing electrodes in contact with the esophageal mucosa[42].

A recent meta-analysis assessing adverse events of EET with most included studies using a combination of RFA and EMR showed an overall adverse event rate of 8.8%. The most noteworthy is stricture formation, which represented 5.6% of all patients, although strictures can almost always be treated safely with endoscopic dilatation with durable response[42,45,85,91,92]. Other serious adverse events included bleeding in 1% and 0.6% rate of perforation. Post-procedural chest pain in the absence of other serious complication occurs in 1.5%–5.4%[42,45,46]. No deaths attributable to endoscopic therapy were recorded[93].

### **Surgery**

En-bloc esophagectomy and lymphadenectomy of the mediastinal and abdominal nodes *via* an abdominal or right transthoracic approach is the standard surgical approach to adenocarcinoma arising within a Barrett's segment[57,73]. For tumors in the distal two thirds of the esophagus, esophagectomy is typically performed with the Ivor-Lewis technique, *via* laparotomy and right thoracotomy. Tumors located in the upper third of the esophagus are typically managed *via* the McKeown technique[58].

Esophagectomy has traditionally been considered a relatively high-risk surgery with significant morbidity and mortality rates. Adenocarcinoma specific 90-d mortality has been reported in up to 8.7% [94]. However, early stage carcinoma limited up to submucosa tends to be associated with much more favorable operative risks. When esophagectomy is performed for such early disease, operative mortality ranges between 0% and 5% (Supplementary Table 4)[54,57,59,75-78,95-97]. Serious adverse events, however, remain relatively common and include anastomotic leaks and tracheal injury[98]. Even when the immediate postoperative course is benign, foregut function is permanently altered, and there can be long-term (and in some cases, permanent) impairment of quality of life due to dysphagia, vomiting, reflux symptoms, abdominal pain, and dumping syndrome[99].

## **THERAPEUTIC EFFICACY**

### **Non-dysplastic Barrett's**

**Endoscopic eradication therapy:** Surveillance with repeat endoscopy every 3–5 years is recommended for non-dysplastic BE[12-14], however there is little data examining ablative therapy. Wani *et al*[22] suggested in a meta analyses that ablative therapies reduced the annual incidence of EAC from 0.60% to 0.16% [22], though the included studies were of varying quality. A single prospective multi-center trial including 50 patients reported complete eradication of intestinal metaplasia rate of 92% at 5 years of follow up. Of the 8% who recurred, all were retreated and eradication of intestinal metaplasia re-achieved. There was no progression to EAC for the duration of the study with no recorded mortalities, serious adverse effects or strictures[90].

Due to the low progression rates of non-dysplastic BE to cancer it is unlikely that any study will ever demonstrate a benefit of ablative therapy in preventing progression to cancer, let alone a mortality benefit. Due to the very low risk profile of non-dysplastic BE, EET is not indicated given that it is not entirely devoid of risk.

### **Barrett's with low grade dysplasia**

**Endoscopic eradication therapy:** The management of LGD-BE is the most controversial aspect of the management of BE. Retrospective data suggested that EET was highly effective in eradicating intestinal metaplasia in LGD-BE[92]. In terms of the efficacy of RFA for preventing progression of LGD-BE to cancer, a systematic review and meta-analysis including 19 studies and a total of 2700 patients found that compared to surveillance, RFA was associated with relative risk of disease progression to HGD or EAC of 0.14[100]. Three randomized controlled trials examining this question have been published to date. The SURF trial compared RFA against surveillance in patients with LGD-BE without visible lesions. Progression to EAC was reduced by 7.4% (1.5% in RFA arm *vs* 8.8% in control arm) over a median 3 year follow up period[45]. Long term, no further EAC occurred in the ablation arm compared with 10.3% rate of cancer observed in the control arm over 73 mo. On intention to treat analysis, the number needed to treat was 11.4 to prevent cancer. Notably, all 23 progressors to HGD or EAC subsequently achieved complete eradication of cancer and dysplasia by the end of the extended study [101]. Subsequently the AIM DYSPLASIA study showed 5% of LGD-BE patients receiving RFA progressed to HGD compared with 14% in the sham arm over the 12-mo study period. No cancers developed in either arm[42]. The study was extended for 3 more years and only 1 subject from the sham arm developed intramucosal adenocarcinoma, which was cured with EMR[91]. However, these studies are limited by roughly half of subjects not reaching their third year of follow up. A recent multi-center RCT by Barret *et al*[46] retained a near entirety of their cohort of 82 patients for up to 3 years and did not show statistical significance in neoplastic progression rates (12.5% RFA *vs* 26.2% surveillance,  $P = 0.15$ ). The most notable finding, and likely explanation for the negative result, was that RFA was much less

effective with significantly lower rates of eradication of dysplasia and intestinal metaplasia (55% and 35% respectively) compared to the earlier studies (Table 3). The lower efficacy of RFA in this study may be attributed to several factors, most importantly a less aggressive protocol (maximum number of ablation sessions was capped at 4). There was a suggestion of a learning curve and operator effect, with significant difference in success rates between low and high-volume centers[46]. Further, this seemed to be a less 'aggressive' cohort of LGD-BE with much lower rate of neoplastic progression, and higher rate of spontaneous remission of LGD-BE, compared to the former studies. There is no data on the surgical efficacy of LGD-BE.

With conflicting findings from high-quality randomized controlled trials, the decision to offer EET for LGD-BE remains nuanced and several factors need to be considered in the decision-making process. Firstly, RFA only provides a benefit when LGD cases are carefully confirmed by expert pathologists to avoid overdiagnosis and identifying a highly select LGD-BE cohort with rates of progression comparable to that typically associated with HGD-BE[42,45]. This is not representative of most patients diagnosed with LGD-BE. Second, a commitment to an aggressive RFA protocol with potential for several sessions (often 4 or more) needs to be made in order for RFA to be successful in reducing risk of cancer progression. Third, it appears that RFA is more likely to be successful in high-volume centers. Fourth, one must bear in mind that when under surveillance by experts, cancers that evolve from LGD-BE tend to be early and appear to be amenable to curable therapy. Therefore, based on available data, one could argue that the long-term outcome for those under surveillance is no worse, even if HGD or cancer developed.

### **Barrett's with high grade dysplasia**

**Endoscopic eradication therapy:** Studies of varying quality demonstrate that RFA reduces annual progression of HGD to EAC to a range between 0.6%–2.4% [22,42,91,102–105] compared to no treatment, which has an estimated rate of 5%–10% as described above. To date, there is one RCT that has randomized RFA of HGD against a control arm. RFA reduced progression to cancer from 19% to 2.4%, and the number needed to treat was six[42]. This trial was extended by 3 more years with cross-over from the sham arm to RFA, leading durable remission and an annual progression rate to EAC of 0.60% [91]. Only one other prospective study recruited 75 consecutive subjects with HGD-BE, finding that all patients who achieved complete eradication of BE with EET had no progression to EAC over a follow up period of 31 mo[85].

Once the threshold of HGD has been reached, subjects are also at risk of developing other areas of HGD within their Barrett's mucosa[50]. Further, those who achieve complete endoscopic eradication of Barrett's mucosa are far less likely to progress to cancer compared to those where this is only partially achieved[85,103–105]. Thus, a logical step is to eradicate all surrounding Barrett's tissue once a diagnosis of HGD has been made. In patients with HGD, EET is effective in eradicating all dysplasia in 79%–97%, and intestinal metaplasia in 51.2%–94% [85,92,96,102–105] (Table 4). Low eradication rates are explained by non-standardized and incomplete RFA treatment sessions[102] and inclusion of treatment-experienced subjects representing resistant disease due to fibrosis[103]. Furthermore, experienced centers and contemporary data report higher rates of complete eradication of dysplasia and intestinal metaplasia above 90% [92]. Haidry *et al* [104] compared early and late cohorts, finding rise in eradication of intestinal metaplasia from 57% to 83% [104].

Therefore, EET is effective in reducing annual cancer progression risk by 5-fold, to approximately 2% by eradicating areas of HGD as well as surrounding Barrett's mucosa. The risk of cancer appears to be reliably attenuated when all residual Barrett's mucosa is completely treated. Overall 5-year survival rate appears to be very high at 90%, even in those who do not achieve complete eradication of Barrett's mucosa[85].

**Surgery:** We can presume individuals have complete eradication of dysplasia and intestinal metaplasia on the day of esophagectomy. Nevertheless, there is paucity of high quality evidence of overall survival and recurrence following esophagectomy for HGD-BE, as most studies are retrospective with small numbers. Five retrospective studies that had referred patients for surgery after biopsy or esophagectomy confirmation of HGD-BE showed promising 5-year survival rates ranging from 83%–97% [97,106–109] with disease free survival at 5 years surpassing 94% in 2 of these studies [106,107]. Another study by Edwards *et al* [110] reported an 82% survival rate after a median of 2.7 years in a small cohort of eleven [110]. These disease free survival rates are not markedly different to those following EET for HGD. However, rates in surgical series incorporate a mixed population, with up to 40% of HGD-BE subjects referred for esophagectomy having evidence of infiltration past the basement membrane corresponding to intramucosal adenocarcinoma [97,106,108,110], reflecting a period where endoscopic assessment was not as accurate as the modern era with subtle lesions likely missed.

Therefore, esophagectomy for HGD shows 5-year overall survival rates above 83% and there is some data to suggest disease-free survival at 5 years exceeds 94%.

### **Intramucosal esophageal adenocarcinoma (T1a)**

**Endoscopic eradication therapy:** Successful endoscopic eradication rates of intramucosal adenocarcinoma is reported to occur in between 82%–100% [75,92,95,96,104,105,111–119]. Pech's large cohort

**Table 3 Efficacy of endoscopic eradication therapy for Barrett's esophagus with low-grade dysplasia**

Ref.	Type	n	CE-IM	CE-D	NNT to prevent disease progression	Annual disease progression, treatment vs placebo (P value)
Wani <i>et al</i> [22]	Meta-analysis	1512	-	-	65.5 (EAC)	0.16% vs 1.7% (P = 0.99) (EAC)
Shaheen <i>et al</i> [42]	RCT	64	81%	90.5%	11.3 (HGD)	5% vs 14% (HGD) (P = 0.33)
Shaheen <i>et al</i> [91]	Retrospective	52	98%	98%	NA	NA
Bulsiewicz <i>et al</i> [92]	Retrospective	41	93%	100%	NA	NA
Phoa <i>et al</i> [45]	RCT	136	88.2%	92.6%	13.6 (EAC)	1.5% vs 8.8% at 3 yr (EAC) (P = 0.03)
Qumseya <i>et al</i> [100]	Meta-analysis	2746	-	-	16 (EAC)	NA
Pouw <i>et al</i> [101]	Retrospective	83	90%	90%	11.4 (EAC)	NA
Barret <i>et al</i> [46]	RCT	82	37.5%	52.5%	-	5% vs 2.4% at 3 yr: (EAC) (P = 0.52)

n: Patient number; CE-D/IM: Complete eradication of dysplasia/intestinal metaplasia; EAC: Esophageal adenocarcinoma; HGD: High grade dysplasia; NNT: Number needed to treat; NA: Not application.

**Table 4 Efficacy of endoscopic eradication therapy for Barrett's esophagus with high-grade dysplasia**

Ref.	Type <sup>1</sup>	n	CE-IM	CE-D	NNT to prevent disease progression	Annual disease progression, treatment vs placebo (P value)
Overholt <i>et al</i> [52]	RCT (PDT)	208	52%	77% (including HGD)	22	3.6% vs 8.14% (P = 0.006)
Ganz <i>et al</i> [102]	Retrospective	92	54%	80%	NA	1.4%
Wani <i>et al</i> [22]	Meta-analysis	236	-	-	20.4	1.7% vs 6.6% (P = 0.02)
Shaheen <i>et al</i> [42]	RCT	63	73.8%	81%	6	2.4% vs 19% (P = 0.04)
Shaheen <i>et al</i> [91]	Retrospective	54	89%	93%	NA	0.6%
Moss <i>et al</i> [85]	Prospective (SRER)	35	94%	94%	NA	Nil
Zehetner <i>et al</i> [96]	Retrospective	22	89%	89.5%	NA	Nil
Okoro <i>et al</i> [103]	Retrospective	35	51.2%	79%	NA	2.3% (2 yr)
Bulsiewicz <i>et al</i> [92]	Retrospective	118	90%	97%	NA	NA
Haidry <i>et al</i> [104]	Retrospective	122	85%	92%	NA	2.5% (3 yr)
Li <i>et al</i> [105]	Retrospective	832	83.4%	92.1%	NA	3% (2.8 yr)

<sup>1</sup>Studies used endoscopic mucosal resection and radiofrequency ablation unless otherwise stated.

CE-D/IM: Complete eradication of dysplasia/intestinal metaplasia; EAC: Esophageal adenocarcinoma; NNT: Number needed to treat; PDT: Photodynamic therapy; SRER: Stepwise radical endoscopic resection; NA: Not application.

involved 1000 prospective patients over a 15-year period with successful endoscopic resection of cancer and HGD in 96.3%. These patients were closely followed up giving rise to a long term remission rate of 93.8% at 5 years[117]. Another prospective study by Phoa *et al*[119] followed 132 subjects with a significant proportion having intramucosal adenocarcinoma. 92% achieved cure of cancer and dysplasia with a quarter of patients reaching 3 year follow up having durable response rate of 95%[119]. A number of other prospective trials have shown successful endoscopic eradication rates of intramucosal adenocarcinoma exceeding 97%[111-115].

Although initial remission rates are promising, long term outcomes may be more relevant. Three prospective studies exceeding 100 subjects show durability rates of 93.8%–100% over a follow up period ranging between 3–5 years[95,111,117]. Remaining data showing endoscopic eradication rates are displayed in Table 5. Despite these limitations it is clear that residual or recurrent EAC is easily managed by further EET[75,95,96,111,112,115,117,119]. Pech *et al*[117] showed retreatment with EET was successful in 115 out of 140 subjects[117]. Further, esophagectomy also appears to remain a valid



**Table 5 Efficacy of endoscopic eradication therapy for Barrett's esophagus with intramucosal adenocarcinoma**

Ref.	Type <sup>1</sup>	n <sup>2</sup>	Eradication of T1a	5-yr OS
Ell <i>et al</i> [111]	Prospective	100	99%	98%
Pech <i>et al</i> [112]	Prospective (EMR +/- PDT)	349; HGD 17.5%	97.4% (including HGD)	NA
Pouw <i>et al</i> [113]	Prospective (RFA +/- EMR)	44; HGD up to 27%	100%	NA
Prasad <i>et al</i> [75]	Retrospective (PDT)	132	94%	83%
Pouw <i>et al</i> [114]	Prospective (EMR + RFA)	24; HGD 25%; T1b 8%	100%	NA
Pech <i>et al</i> [95]	Retrospective (EMR +/- APC)	79	98.7%	96%
Van Vilsteren <i>et al</i> [115]	RCT	47; HGD up to 40%	97.9%	NA
Zehetner <i>et al</i> [96]	Retrospective	18	82% (14/17); 3/17 subsequently successfully treated under surveillance	NA
Bulsiewicz <i>et al</i> [92]	Retrospective	29	93%	NA
Ngamruengphong <i>et al</i> [120]	Retrospective	229; HGD 24%	-	60%
Saligram <i>et al</i> [116]	Retrospective	54	96%	89% (over 2 yr)
Pech <i>et al</i> [117]	Prospective	1000	96.3% (including HGD)	91.5%
Haidry <i>et al</i> [104]	Retrospective	63	97.5% (combined with HGD cohort)	NA
Agoston <i>et al</i> [118]	Retrospective	79	86%	NA
Li <i>et al</i> [105]	Retrospective	162	97.5%	NA
Phoa <i>et al</i> [119]	Prospective	132; ND/LGD 8.4%; HGD 30%; T1b 1.7%	92%	NA
Marino <i>et al</i> [121]	Retrospective	856	-	71.8%
Semenkovich <i>et al</i> [74]	Retrospective	1123	-	70%

<sup>1</sup>Studies use endoscopic mucosal resection/radiofrequency ablation unless otherwise stated.

<sup>2</sup>Pure T1a cohort unless otherwise stated.

n: Patient number; APC: Argon plasma coagulation; OS: Overall survival; PDT: Photodynamic therapy; NA: Not application.

treatment option for treatment failures with minimal risk of lymph node metastasis[75,115-117,119].

Reported survival rates of subjects with intramucosal adenocarcinoma who have undergone EET are between 60%-100%[74,75,95,111,120,121]. Lower survival rates are felt to be secondary to selection bias in these observational studies whereby those with frailty, age and comorbidities are more likely to receive less invasive EET than surgery[74,120]. Further, deaths are predominantly due to causes unrelated to EAC[75,95,112,115-117], for example, Pech *et al*[117] reported only 2 in 1000 subjects with tumor-associated deaths[117].

Intramucosal adenocarcinoma can be successfully treated with EET in greater than 90% of cases with durable remission in the vast majority. 5-year overall survival is an estimated 80%, with deaths predominantly attributable to other causes.

**Surgery:** There are several large surgical series reporting overall survival rates whose findings are severely limited by lack of data on follow up protocols, imaging modalities for surveillance and comorbidities[54,74]. However, at least eight good quality retrospective studies with follow up of 4 years or more reported estimated 5-year overall survival between 73%-93% (Table 1)[55-57,59,72,75,95,97]. The largest of these retrospective studies contained 75 subjects with intramucosal adenocarcinoma from a single center with detailed follow up protocol over a median duration of 50 mo. The 5-year overall survival rate was 92% with 5 year disease specific survival an estimated 98%[55].

Surgery provides definitive therapy of cancer as well as Barrett's mucosa leading to high 5-year overall survival rates of approximately 80%. Most deaths are attributable to non-EAC related causes and correlate to even greater rates of disease-free survival approaching 100%.



### **Submucosal esophageal adenocarcinoma**

**Endoscopic eradication therapy:** There are no prospective or randomized controlled studies that assess the survival benefit of endoscopic therapy for submucosal adenocarcinoma. Endoscopic eradication of submucosally invasive adenocarcinoma is reportedly achieved in 63%-100% following EET[77,81,122] (Table 6). Manner *et al*[81] retrospectively studied efficacy of EET in 61 subjects with low risk submucosal disease, defined as macroscopically polypoid or flat, minor invasion depth into the submucosa, good to moderate differentiation and with no lymphovascular invasion. Cancer eradication was achieved in 87% and durable response was sustained in 83.6% over a mean reaching 4 years. 5-year overall survival was 84%. Only 1 patient required esophagectomy for lymph node metastasis found during surveillance after complete endoscopic remission was achieved[81]. However, this study and others did not uniformly apply ablative therapy following endoscopic resection[77,81,122], thus possibly underreporting true eradication rates. When disease recurrence occurs after initial EET, successful retreatment appears to be achievable with minimal risk of lymph node metastasis[81,122].

Of 5-year overall survival rates of submucosal adenocarcinoma undergoing EET range from 50%-87% [74,77,81]. Low survival rates were associated with several factors including high risk histological features and extensive comorbidities, with EET often performed in patients deemed unfit for surgery with the majority of subsequent deaths attributable to other causes[77,78].

Complete eradication of cancer may be achievable in up to 87% in low risk submucosal adenocarcinoma. Reported overall survival is very low, though this primarily relates to the frail and comorbid demographic that typically is selected for EET. There remains a role for endoscopic therapy with curative intent in low-risk submucosal disease. Especially in those with comorbidities, EET is a reasonable option in the setting of low-risk histological features.

**Surgery:** There are numerous retrospective studies of varying size and quality that report overall survival and recurrence rates of submucosal EAC. 5-year overall survival rates for submucosal adenocarcinoma range between 58%-89% [55-57,59,61,72,76,77,97]. Four studies report 5-year disease free survival rates between 60%-92% [57,59,61,77], with contemporary series typically reporting higher overall and cancer-specific survival rates [56,59,61,72,97]. Disease-free survival is typically significantly higher than overall survival given the high rates of non-cancer related deaths in this cohort [61,72,78]. Esophagectomy appears effective in treating submucosal tumors regardless of the presence of high risk features. Otaki *et al* [77] showed a 5-year overall survival rate of 89% despite the majority of patients having at least 1 high risk feature [77].

Surgery appears to be a very effective and curative option in submucosal EAC. Survival rates may reach up to 80% in appropriate surgical candidates, with a significant portion of deaths being unrelated to EAC.

## **CONCLUSION**

### **Non-dysplastic Barrett's**

We recommend surveillance endoscopy for patients with non-dysplastic BE. EET is not justified in non-dysplastic BE due to the extremely low rates of cancer progression (Table 7).

### **Barrett's with low grade dysplasia**

We recommend that LGD be always confirmed by expert gastrointestinal pathologists. If confirmed, such patients should all enter a close surveillance program at a high-volume specialized Barrett's center. EET can be offered, as long as the following caveats are understood: (1) Only a small minority will progress; (2) Benefit of RFA seems confined to aggressive RFA protocols performed in expert centers; (3) It appears that in patients under surveillance by expert hands any progression to HGD or cancer can be detected early and completely treated without any adverse consequences; and (4) Adverse events occur following RFA in an estimated 10%, however rarely severe.

### **Barrett's with high grade dysplasia**

After the confirmation of HGD-BE by expert gastrointestinal pathologists, we recommend referral to an expert Barrett's center with repeat endoscopy within 4 wk of diagnosis. We recommend all visible lesions be treated with EMR initially which provides additional staging information, followed by sequential RFA until eradication of all visible intestinal metaplasia is achieved. HGD-BE without visible lesions should commence treatment with RFA. The risk of lymph node metastasis is negligible in HGD-BE [68], and surgery should not be offered.

### **Intramucosal adenocarcinoma of the esophagus**

We recommend EET for management of intramucosal adenocarcinoma over surgery. While the literature suggests that cancer-free survival may be modestly higher for surgery, EET is far less morbid, recurrences following EET can usually be managed endoscopically, and for persistent failures salvage

**Table 6 Efficacy of endoscopic eradication therapy for Barrett's esophagus with submucosal adenocarcinoma**

Ref.	Type	n	Eradication of cancer	Survival
Manner <i>et al</i> [81]	Retrospective	61	87% (including HGD)	5-yr OS 84%
Ngamruengphong <i>et al</i> [120]	Retrospective	39	-	5-yr OS 66%
Schölvinck <i>et al</i> [78]	Retrospective	43	-	Median survival: 46 mo
Künzli <i>et al</i> [122]	Retrospective (RFA or APC)	35	100%	-
Semenkovich <i>et al</i> [74]	Retrospective	588	-	5-yr OS 50%
Otaki <i>et al</i> [77]	Retrospective (RFA/APC/Cryo)	73	63% (including HGD)	5-yr OS 59%

APC: Argon plasma coagulation; Cryo: Cryotherapy; HGD: High grade dysplasia; OS: Overall survival; RFA: Radiofrequency ablation.

**Table 7 Recommendations for non-invasive Barrett's esophagus**

Stage	Annualized risk of cancer	Recommended management	Risks of intervention	Post-intervention cancer risk
NDBE	0.5%	Surveillance	Negligible	NA
LGD <sup>1</sup>	1%–3%	Surveillance or EET	Stricture 6%; Chest pain 5%; Bleeding 1%; Perforation 1%	1% per year
HGD	5%–10%	EET	Stricture 6%; Chest pain 5%; Bleeding 1%; Perforation 1%	2% per year

<sup>1</sup>Low grade dysplasia diagnosed by an expert gastrointestinal pathologist.

HGD: High grade dysplasia; EET: Endoscopic eradication therapy; LGD: Low grade dysplasia; NDBE: Non-dysplastic Barrett's esophagus; NA: Not application.

**Table 8 Recommendations for invasive adenocarcinoma arising from Barrett's esophagus**

Invasive Barrett's esophagus by stage	Risk of nodal metastases	Recommended management	Risks of intervention	5-yr disease free survival	5-yr overall survival
Intramucosal adenocarcinoma	2%–4%	EET	Stricture 6%; Chest pain 5%; Bleeding 1%; Perforation 1%	NA	Estimated 80%
Submucosal adenocarcinoma	14%–41%	Surgery	Mortality 3%; Adverse events up to 62%; Long-term symptoms due to altered upper gut function	Estimated 70%	Estimated 75%

EET: Endoscopic eradication therapy; NA: Not application.

esophagectomy is not precluded. Where high-risk histological features are present, surgery may be a greater consideration (Table 8).

### **Submucosal adenocarcinoma of the esophagus**

We recommend surgery as standard therapy for submucosal adenocarcinoma due to high risk of lymph node metastasis. The role of EET is confined to comorbid or elderly patients at high surgical risk, especially where there are low risk histological features.

## **FOOTNOTES**

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