8 Role of Endoscopy in the Diagnosis, Staging, and Management of Esophageal Cancer

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Introduction

The incidence of esophageal adenocarcinoma (EAC) has increased approximately 700% since the late 1970s, outpacing the rate of growth of other major epithelial malignancies [1]. Over 10,000 cases are now diagnosed annually in the USA and most patients do not live more than 5 years after diagnosis [2, 3]. Meanwhile, the incidence of esophageal squamous cell carcinoma (SCC) has declined over several decades [1]. While SCC has no known premalignant condition amenable to screening, EAC is preceded by Barrett's esophagus (BE) in a metaplasia-dysplasia-carcinoma sequence. Barrett's esophagus has been a target for screening efforts and eradication via endoscopic approaches in order to detect and prevent progression to EAC. The risk of developing EAC among patients with untreated Barrett's esophagus is approximately 0.4–0.5% per year [4]. Multiple risk factors such as male gender and long-segment Barrett's esophagus increase the risk of progression [5]. The relatively good 5-year prognosis in early-stage disease compared with advanced stages has led to efforts aimed at the early detection of esophageal cancer in Barrett's esophagus [6, 7]. The use of endoscopy for the prevention, diagnosis, and treatment of esophageal cancer continues to evolve.

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Screening for Barrett's Esophagus

The relatively low prevalence of Barrett's esophagus among patients with gastroesophageal reflux disease (GERD), the current lack of reliable methods for identifying high-risk individuals, and the risk and cost associated with upper endoscopy make population-based screening for Barrett's with upper endoscopy imperfect. The American Gastroenterological Association (AGA) in 2011 recommended endoscopic screening for Barrett's esophagus in patients with multiple risk factors for esophageal adenocarcinoma. These risk factors include age greater than or equal to 50 years, male sex, Caucasian race, chronic GERD, presence of a hiatal hernia, elevated body mass index (BMI), and intra-abdominal distribution of body fat (Table 8.1). This recommendation was graded as weak with moderate-quality evidence, underscoring the lack of consensus in this area.

The British Society of Gastroenterology (BSG) in 2014 recommended screening patients with chronic GERD symptoms plus three of the following: age 50 years or greater, Caucasian race, male gender, and obesity (Table 8.1). They suggest that the threshold to screen for BE should be lowered if there is a family history with one first-degree relative with BE or esophageal adenocarcinoma (grade C recommendation) [8]. While current screening efforts focus on patients with GERD symptoms, BE is known to be present in patients without GERD, and up to 57% of patients with esophageal adenocarcinoma never report typical symptoms of GERD [9, 10]. Some studies have shown that the current practice of using endoscopy after 5 years of GERD symptoms may detect only a limited number of patients who are actually at risk for progression to esophageal adenocarcinoma [4, 11]. The American College of Gastroenterology (ACG) in 2016 continues to recommend against screening for Barrett's esophagus in the general population as noted in the 2008 guidelines but has added a focus on screening men with ≥5 years of GERD symptoms with two additional risk factors [12]. Screening is less emphasized in women with chronic GERD in the absence of multiple risk factors due to a lower risk of EAC.

A case-control study of 63 patients with esophageal adenocarcinoma found that laryngopharyngeal reflux symptoms, such as asthma, aspiration, and hoarseness, might be more prevalent in those with EAC than typical GERD symptoms. Chronic cough was found to be an independent risk factor for EAC, and some have suggested that it may be helpful for screening purposes in identifying people at risk [13].

The low overall incidence of high-grade dysplasia (HGD) and intramucosal carcinoma (IMC) disfavors population-based screening with conventional endoscopy [4, 14–16]. Efforts are underway to identify screening methods that may be more broadly applicable. Unsedated examinations and non-endoscopic options utilizing cytology or capsule esophagoscopy are being evaluated [17, 18]. A veteran population with or without GERD symptoms was randomized to unsedated transnasal esophagoscopy (TNE) or capsule esophagoscopy (ECE) to evaluate BE screening and 12.6% of those randomized to TNE crossed the minimal clinically important threshold for overall procedure tolerability as opposed to none randomized to ECE ($p = 0.001$) [19]. A study involving 96 patients assessing the accuracy and feasibility of unsedated exams with disposable endoscopes compared to conventional upper

Table 8.1 Screening and surveillance endoscopy

	AGA 2011 [5]	ASGE 2012 [119]	BSG 2014 [8]	ACG 2016 [12]	ESGE 2017 [33]
Screening endoscopy	White male, age >50 years, GERD, hiatal hernia, obesity	GERD >5 years, white, male, age >50 years, family history of BE or EAC	Chronic GERD symptoms +3: (50 years or older, white, male, obese). Screening threshold lower for family history of BE or EAC in first degree relative	Men with >5 years and/or frequent (weekly or more) symptoms of GERD (heartburn or acid regurgitation) and two or more risk factors for BE or EAC. RF: age >50 years, Caucasian race, central obesity (waist circumference >102 cm or waist-hip ratio >0.9), current or past history of smoking, confirmed family history of BE or EAC (in first-degree relative)	>5 years GERD, multiple risk factors (age ≥50 years, white race, male sex, obesity, first-degree relative with BE or EAC
Surveillance endoscopy					
No dysplasia on 2 exams	3–5-year interval	3-year interval	2–3 years if max segment length ≥3 cm; 3–5 years if max length <3 cm	3–5-year interval Repeat in 1–2 years if suspected BE but no dysplasia detected	≥1 cm < 3 cm: 5-year interval - ≥3 and <10 cm 3-year interval ≥10 cm: Refer to BE expert center
LGD	Every 6–12 months	Repeat within 6 months, then every 12 months. Consider ablation	Every 6 months	Every 12 months	Every 6 months until no dysplasia and then every 1 year
HGD surveillance	Every 3 months if no eradication therapy	Endoscopic ablation	Multidisciplinary team discussion. Typically endoscopic ablation	Endoscopic management	Every 3 months if repeat biopsy is negative for dysplasia. Treat with RFA if HGD on repeat

ACG American College of Gastroenterology, AGA American Gastroenterological Association, BSG British Society of Gastroenterology, ASGE American Society for Gastrointestinal Endoscopy, ESGE European Society of Gastrointestinal Endoscopy, GERD gastroesophageal reflux disease, BE Barrett's esophagus, EAC esophageal adenocarcinoma, LGD low-grade dysplasia, HGD high-grade dysplasia, EMR esophageal mucosal resection, APC argon plasma coagulation, PDT photodynamic therapy, RF radiofrequency ablation

endoscopy found a moderate level of diagnostic agreement between the two modalities, with Kappa coefficients of 0.409 for erosive GERD and 0.617 for Barrett's esophagus [20]. The procedure was well tolerated, fast, and considered safe. In a study of 121 patients undergoing conventional endoscopy and unsedated small-caliber endoscopy, 71% indicated that they would prefer to have unsedated small-caliber endoscopy performed [17]. In this study, BE was found in 26% of the population undergoing conventional endoscopy and in 30% of those undergoing unsedated endoscopy. The level of diagnostic agreement was moderate with a Kappa of 0.591. An ingestible esophageal sampling device coupled with immunocytochemistry for trefoil factor 3 is being studied as a non-endoscopic screening modality for BE. A study with 504 patients found a sensitivity of 90% and specificity of 93.5% for identifying Barrett's 2 cm or longer when compared to conventional upper endoscopy [21]. A study in 2015 attempted to determine whether a minimally invasive cell sampling device, the Cytosponge, coupled with immunohistochemical staining for the biomarker Trefoil Factor 3 (TFF3), may be able to select patients who need endoscopy for BE screening. The study involved 11 UK hospitals with 1110 patients and found that 93.9% successfully swallowed the Cytosponge without any serious adverse events. The Cytosponge was also favorably rated compared to upper endoscopy ($p < 0.001$). The test sensitivity was found to be 79.9% (95% CI 76.4%–83.0%) which increased to 87.2% (95% CI 83.0%–90.6%) in patients with ≥3 cm of circumferential BE. The specificity for diagnosing BE was 92.4% (95% CI 89.5%–94.7%) [22].

Surveillance

The rate of progression to cancer in non-dysplastic BE was initially thought to be close to 1% per year in small studies [23]; however, subsequent studies have suggested a rate of progression to cancer as low as 0.12% per year [24]. The ACG and AGA estimate the likely rate of progression to cancer to be around 0.2–0.5% per year [5, 12].

The goal of endoscopic surveillance in Barrett's esophagus is to detect dysplasia, especially HGD and IMC, which can be treated through endoscopic measures before progression to invasive adenocarcinoma or metastatic disease occurs. The AGA recommends using high-resolution endoscopes (>850,000 pixels) when examining BE. The availability of this technology has allowed endoscopists to better identify areas of concern within the Barrett's epithelium and to improve biopsy targeting of suspicious lesions. After obtaining targeted biopsies, 4-quadrant biopsies are taken every 1–2 cm for patients with non-dysplastic BE and every 1 cm for patients with dysplastic BE (whether high grade or low grade). This protocol has become the standard of care though questions arise regarding the time and cost involved with the extensive sampling and subsequent interpretation. Some research has suggested that large-capacity or jumbo biopsy forceps may also increase the amount of tissue acquired and the detection of dysplasia [25]. Use of a systematic protocol for biopsies has been shown to be more effective in detecting BE and

dysplasia in BE [26]. The presence of dysplasia should be confirmed by two expert pathologists [5]. Surveillance endoscopy for BE is performed based on the highest degree of dysplasia present. If no dysplasia is identified initially, a second endoscopy with protocol-based biopsies as above should be performed within 1 year. Subsequent surveillance endoscopy should be performed every 3 years for non-dysplastic Barrett's esophagus (Table 8.1) [27].

When BE is identified, control of acid reflux is indicated. Reduction of inflammation with a proton pump inhibitor (PPI) may improve visual recognition of a lesion or nodule on surveillance endoscopy and could theoretically interfere with carcinogenesis [27]. Biopsies from each segment of BE should be submitted to pathology in separate containers to better focus future treatment in areas of concern if dysplasia is discovered.

BE is classified endoscopically according to the Prague classification, using C for the circumferential segment and M for the maximal length of involvement [28]. The length of circumferential Barrett's from the gastroesophageal (GE) junction is recorded, as is the length of the maximal extent of Barrett's extending proximally from the lower esophageal sphincter. There is good interobserver agreement in using these criteria [12, 28], and the approach provides a clear method of communicating the extent of the Barrett's involvement.

If low-grade dysplasia (LGD) is identified, another endoscopy should be performed within 6 months to confirm the degree of dysplasia. Surveillance endoscopy should then be performed every year until no dysplasia is identified on two consecutive exams (Table 8.1) [27]. Recent data have suggested a benefit with radiofrequency ablation (RFA) for low-grade BE, and this practice is becoming more established [29, 30]. The current approach for BE with high-grade dysplasia is to treat with RFA for flat Barrett's esophagus with high-grade dysplasia. Other options including esophagectomy and continued surveillance with upper endoscopy every 3 months may be considered in some circumstances. Endoscopic mucosal resection should be performed for areas of nodularity and mucosal irregularity prior to initiating RFA [31, 32].

The BSG has several similarities in its surveillance guidelines compared to those of the AGA and ACG (Table 8.1). They recommend surveillance every 2–3 years for non-dysplastic BE (ND-BE) if the maximum segment length is greater than or equal to 3 cm and 3–5 years if the maximum segment length is less than 3 cm. They also recommend surveillance with endoscopy every 6 months if LGD is discovered until two consecutive exams show non-dysplastic BE. When HGD or carcinoma is discovered, they recommend discussion with the patient and a multidisciplinary team (MDT) determination for surveillance intervals and treatment. The MDT should include an interventional endoscopist, gastrointestinal pathologist, radiologist, and surgeon. This team should consider factors such as comorbidities, nutritional status, patient preference, and staging. They suggest an outpatient discussion regarding the morbidity and mortality related to the potential treatment options, long-term survival, and quality of life [8].

The European Society of Gastrointestinal Endoscopy (ESGE) in 2017 recommends surveillance depending on the size of non-dysplastic BE lesion discovered:

5-year interval for ≥1 cm <3 cm disease, 3-year interval for ≥3 and <10 cm disease, and disease ≥10 cm requiring referral to a BE expert center. For LGD they recommend surveillance every 6 months until no more dysplasia is found and then every 1 year thereafter. For HGD they recommend surveillance every 3 months if repeat biopsy is negative for dysplasia and to treat with RFA if HGD is found on repeat endoscopy [33].

A study from the Netherlands Cancer Registry compared patients participating in a surveillance program for BE before EAC diagnosis with those not participating in such a program between 1999 and 2009 [1]. Two-year and five-year mortality rates were lower in patients undergoing adequate surveillance (adjusted hazard ratio (HR) = 0.79, 95% confidence interval (CI) = 0.64–0.92) when compared with patients with a prior BE diagnosis who were not participating. This study suggested that there is a mortality reduction from EAC if adequate surveillance for BE is performed.

There are many novel and advanced imaging modalities being incorporated into surveillance endoscopy, including narrow band imaging, confocal laser endomicroscopy, and optical coherence tomography. The technologies might improve targeting and detection. While early studies suggest utility, these advanced imaging modalities are currently being studied primarily in specialty centers and academic institutions. Broader adoption may await standardized diagnostic criteria for differentiating ND-BE, LGD, and HGD [34].

Endoscopic Treatment of Gastroesophageal Reflux Disease

Gastroesophageal reflux disease (GERD) has been implicated in the development of BE, and multiple endoscopic approaches have been studied to control GERD. Some trials have been disappointing and thus far no one endoscopic modality has emerged as a standard. One device involves the use of radiofrequency energy delivered through a catheter equipped with a flexible balloon-basket assembly with four electrode needle sheaths [35]. Radiofrequency energy is delivered at varying levels from the lower esophageal sphincter to the gastric cardia. This procedure was approved by the FDA in 2000 [36]. The endoscopic treatment is performed with sedation and is typically an outpatient procedure [37]. The procedure may lead to collagen deposition at the gastroesophageal junction (GEJ) and may increase lower esophageal sphincter (LES) pressure. It is thought that the procedure also has neuromodulatory effects from selective neurolysis of vagal afferents leading to reduced transient LES relaxations. The ablation may also decrease the perception of heartburn pain due to the influence on sensory nerves as well as reduce reflux [38–40].

Another device involves an endoluminal gastroplication with suture placement at the LES for reduction of symptoms. It was also approved by the FDA in 2000 [41]. Its function is to mechanically restore a barrier against reflux. There is some data suggesting that there is a decrease in esophageal sensitivity to acid after placement of the sutures [37, 42, 43]. Other endoscopic gastroplication devices creating layered full thickness plications of the wall of the cardia have been described [44].

Another endoscopic anti-reflux device creates a transoral incisionless esophagogastric fundoplication (TIF). It creates an anterior partial fundoplication by attaching the fundus of the stomach to the anterior and left lateral wall of the distal esophagus. Patients with moderate to severe GERD or those who are partially responsive to PPIs may benefit from treatment. Contraindications include BMI greater than 35 kg/m^2, Barrett's esophagus, esophageal varices, hiatal hernia greater than 2 cm, and major connective tissue disorders [45, 46].

A non-absorbable ethylene-vinyl-alcohol polymer which was injected into the musculature or deep submucosa of the LES where it solidified into a sponge-like implant to increase the LES pressure was previously described [47–49]. The device was voluntarily recalled in 2005 due to major reported side effects.

In summary, some data suggest that radiofrequency energy produces an improvement in GERD symptoms and quality of life with negligible morbidity [50–52], and that this approach has a good safety profile and low complication rate (<0.07% by 2006) [53]. There continues to be active development in plicating devices for the endoscopic treatment of GERD. Other systematic reviews have reviewed endoluminal therapies for the treatment of gastroesophageal reflux [54]. Especially in the presence of a large hiatal hernia, laparoscopic nissen fundoplication remains a very effective approach.

Diagnosis of Barrett's Esophagus and Esophageal Adenocarcinoma

Upper Endoscopy for Tissue Diagnosis

The standard approach for the diagnosis of esophageal adenocarcinoma and Barrett's esophagus involves visually directed biopsied obtained at an upper endoscopy. For Barrett's esophagus, the Seattle protocol involves 4-quadrant biopsies every 1–2 cm under white light endoscopy with a goal of detecting dysplasia [55]. The BSG Guidelines published in 2014 recommend a 2 cm biopsy interval protocol in addition to the sampling of any visible lesions (BSG Grade B). They state that adherence to this method is variable (10–79%), with lower adherence for longer segments. Lower adherence may contribute to less dysplasia detection [56–58].

To establish the diagnosis of BE, endoscopic and histologic criteria must be met. Endoscopic criteria include displacement of the Z-line (the squamocolumnar junction) proximal to the GEJ, identified by the pinch of the lower esophageal sphincter. In BE, salmon-colored Barrett's mucosa extends proximally and is distinguished from the pale, glossy appearing squamous mucosa [59]. Pathologic criteria include the presence of intestinal metaplasia with goblet cells in the mucosa. Because of the implications for management, the diagnosis of dysplasia or adenocarcinoma should be confirmed by two expert histopathologists [8]. However, even experienced gastrointestinal pathologists may disagree on a diagnosis of HGD and intramucosal adenocarcinoma [60]. Nodularity and mucosal irregularity within the Barrett's epithelium are more likely to contain dysplasia or carcinoma and should be targeted with focal biopsy or removed with endoscopic mucosal resection (EMR). Flat and

occult lesions may be easier to detect with specialized modalities such as narrow band imaging [55].

Advanced Modalities to Improve Detection

Narrow Band Imaging

Narrow band imaging (NBI) is a high-resolution endoscopic technique that enhances the imaging of the fine structure of the mucosal surface without requiring the instillation of staining agents. It involves the use of selective wavelengths of light [55]. The depth of penetration of light directly correlates to its wavelength, and increased depth of light penetration leads to a similar increase in wavelength of visible light. For instance, the blue light used in NBI allows optimal superficial imaging [61], while red light has longer wavelengths and penetrates deeper. The blue light (415 nm) and green light (540 nm) of NBI are absorbed by hemoglobin and demonstrate superficial vasculature [62]. NBI may be preferred in some settings to chromoendoscopy, which involves instillation of a dye such as methylene blue to stain the mucosa in the gastrointestinal tract for enhanced visualization. The dye in chromoendoscopy requires formulation and attention to application and may not distribute evenly over the mucosa.

A meta-analysis of eight studies including 446 patients and 2194 lesions demonstrated that the sensitivity and specificity for detecting HGD with NBI with magnification were 96% and 94%, respectively. The sensitivity for IMC was 95% and the specificity was 65% [63]. A randomized crossover trial of 123 patients showed that NBI without magnification identified a higher proportion of patients with dysplasia compared to white light (30% vs. 21% with $p = 0.0001$) [64]. A similar number of patients found to have IMC were discovered with the use of fewer biopsies using NBI compared to white light (3.6 vs. 7.6 with $p = 0.0001$). However, interobserver agreement regarding interpretation of NBI images of IMC and dysplasia between expert and nonexpert endoscopists may be low [65–67]. NBI does not increase cost or add any significant risk and requires a negligible amount of time and is therefore often considered a standard part of the endoscopic examination in Barrett's esophagus.

Confocal Laser Endomicroscopy

Confocal laser endomicroscopy (CLE) uses a low-power laser to illuminate tissue and detects the reflected fluorescent light. The laser is directed at a certain depth and light is reflected back through a very thin focal plane, refocused, and passed through the confocal aperture which enhances spatial resolution. Scanning is performed in both the horizontal and vertical planes and an in vivo microscopic image of biological tissue is produced. White-light endoscopy and CLE are performed together with images displaying simultaneously. It provides gray-scale imaging of tissue microstructures at or near the level of histopathology. These images may be at 1000-fold magnification [68]. An endoscope-based system (eCLE) (Optiscan Pty., Ltd.,

Notting Hill, Australia; Pentax) for CLE is no longer on the market. The probe-based system (pCLE) passed through the working channel of the endoscope is in use (Cellvizio; Mauna Kea Technologies, Paris, France) [55].

One study using the Mainz criteria (confocal Barrett's classification system) demonstrated a sensitivity and specificity of 98% and 94% for BE and 93% and 94% for BE-associated dysplasia, respectively, in predicting in vivo histology [69]. Strong inter-observer and intra-observer agreement was reported using this classification system (kappa 0.84 and 0.89, respectively). A randomized controlled study involving 192 patients with BE compared high-definition white-light endoscopy (HD-WLE) with random biopsies to endoscopy plus eCLE with targeted biopsies. In this study, the combination of HD-WLE and eCLE increased the diagnostic yield of biopsies for neoplasia (22% vs. 6%) and significantly lowered the number of biopsies required [70]. A multicenter study of 101 patients suggested that adding pCLE to HD-WLE significantly improved the detection of neoplasia; sensitivity and specificity with HD-WLE alone were 34.2% and 92.7%, respectively, compared to 68.3% and 87.8% with combined pCLE and HD-WLE ($p = 0.002$ and $p < 0.001$) [71]. Another smaller study did not show as promising results with 68 patients in three centers when assessing pCLE vs. WLE. Specificity and negative predictive value were low at 12% and 18%, respectively [72]. A recent meta-analysis comparing NBI and CLE for detecting neoplasia in BE suggested that CLE significantly increased the per-lesion detection rate for esophageal neoplasia, HGD, and EAC in BE patients. Of the five studies including 251 patients, the pooled additional detection rate (ADR) of CLE for per-lesion detection of neoplasia was 19.3% (95% CI: 0.05–0.33, $I^2 = 74.6\%$). The pooled sensitivity of NBI was not significantly lower than that of CLE and the pooled specificities were similar [73]. While CLE offers the promise of real-time histology, caveats include the fluorescein administration, cost, small field of view, and learning curve. Further investigation may better define the role for the technology [55].

Optical Coherence Tomography

Optical coherence tomography (OCT) is similar to ultrasound technology but uses light waves in place of sound. It creates a cross-sectional image of tissue using infrared light by penetrating up to 3 mm in depth using a catheter through a standard endoscope. It does not require the administration of fluorescein. The intensity of the back-scattering of light creates cross-sectional and 3-dimensional images of tissue microstructures. The images are similar to coarse black and white histopathology. OCT does not require contact with esophageal tissue and can visualize the epithelium, basement membrane, vasculature, and lamina propria. Nuclear dysplasia cannot be observed [74]. A prospective study involving 33 patients with BE demonstrated the accuracy in the detection of dysplasia in BE. The sensitivity and specificity of OCT for detecting dysplasia were 68% and 82% [75], respectively, and the diagnostic accuracy for the four endoscopists involved ranged from 56 to 98%. Computer-aided diagnosis (CAD) algorithms might increase accuracy of detection of dysplasia and metaplasia. A recent study used histology as a reference standard and developed

a CAD algorithm with a sensitivity of 82%, specificity of 74%, and accuracy of 83% for detecting dysplasia in BE [76]. OCT is not currently widely available [77].

A study assessing the presence of dysplasia in BE looked at 177 biopsy-correlated images to evaluate a novel dysplasia index using OCT image characteristics of IMC and HGD in Barrett's esophagus. The sensitivity and specificity rates for diagnosing HGD/adenocarcinoma were 83% and 75%, respectively. There was significant correlation between diagnoses of IMC/HGD by histopathology and scores for the image features including dysplasia, surface maturation, and gland architecture [78].

Endoscopic Mucosal Resection for Diagnosis

Endoscopic mucosal resection (EMR) is recommended for patients with Barrett's esophagus with nodules, raised lesions, or mucosal irregularity. With EMR, a specialized cap is affixed to the end of an endoscope, and tissue is suctioned into the cap. A band is deployed at the base to create a pseudopolyp of tissue. The tissue is then removed using snare electrocautery. This technique allows the removal of an approximately 1 cm area of mucosa and a portion of the underlying submucosa for histologic examination. Repeated contiguous EMR may be performed to resect a larger area of tissue (piecemeal EMR). EMR provides a much larger tissue specimen for examination by pathologists than traditional forceps biopsy. It is more likely to detect cancer or dysplasia, and it allows pathologists to define the precise depth of invasion in early cancers for staging [59]. The technology was originally developed as a diagnostic procedure in the 1980s and has now evolved into an effective therapeutic modality as well [6].

In a retrospective analysis involving 35 patients with BE undergoing both EMR and mucosal tissue biopsy, 63% of specimens were discordant [79]. Fifty-three percent of biopsy results were upstaged with EMR, and the most common change was an upstaging to invasive adenocarcinoma. Approximately 10% of biopsy specimens were downstaged via examination of EMR specimens. Of the 13 cases of invasive adenocarcinoma discovered through EMR, 92% were upstaged, leading to management change in 34% of cases. Another study demonstrated that EMR changed the grade or T-stage in 48% of patients when compared to traditional biopsies. EMR has also been employed in eliminating the affected Barrett's segment in 94% of cases and has been shown to reduce the need for esophagectomy [80]. EMR is a critical component in the accurate staging and proper management of BE-related lesions (Figs. 8.1 and 8.2).

EMR may also help to diagnose invasive squamous cell carcinoma. In one study, 51 patients diagnosed with high-grade intraepithelial squamous neoplasia upon biopsy after endoscopic iodine staining were evaluated with EMR for comparison of results [81]. Histologic examination of EMR specimens showed that 23.5% (12/51) had tumor invasion of the lamina propria and 7.8% (4/51) had muscularis mucosa invasion. The other 68.6% (35/51) had confirmed high-grade intraepithelial squamous neoplasia. Follow-up was a median of 23 months with two recurrences both needing a second EMR. Per 2016 ACG guidelines, patients with LGD and HGD should have EMR performed if mucosal abnormalities are present [12].

Staging

Endoscopic Ultrasound for Locoregional Staging

Endoscopic ultrasound (EUS) is the procedure of choice to establish the depth of invasion and lymph node (LN) status and is the most accurate tool for the TNM staging of esophageal neoplasia [82]. EUS is preceded by a careful upper endoscopic examination which provides information about the location of the disease, the extent of the background Barrett's epithelium, and also may reveal features such as gastric extension and the presence of a hiatal hernia. EUS establishes the T-stage by visualizing the wall layers and defining the depth of invasion. EUS does not visualize nuclear and cellular changes [83], and with early-stage N0 disease, an EMR may be performed for pathologic examination to establish the precise T-stage, grade, and histopathologic features such as lymphovascular invasion. EUS may not be required for HGD and small intramucosal tumors before endoscopic or surgical treatment [55].

The main use of EUS in Barrett's-related disease has been the detection of invasive tumors and the presence of lymph node metastases (LNM). This can allow ablative therapy in those with disease limited to the mucosa and select submucosal

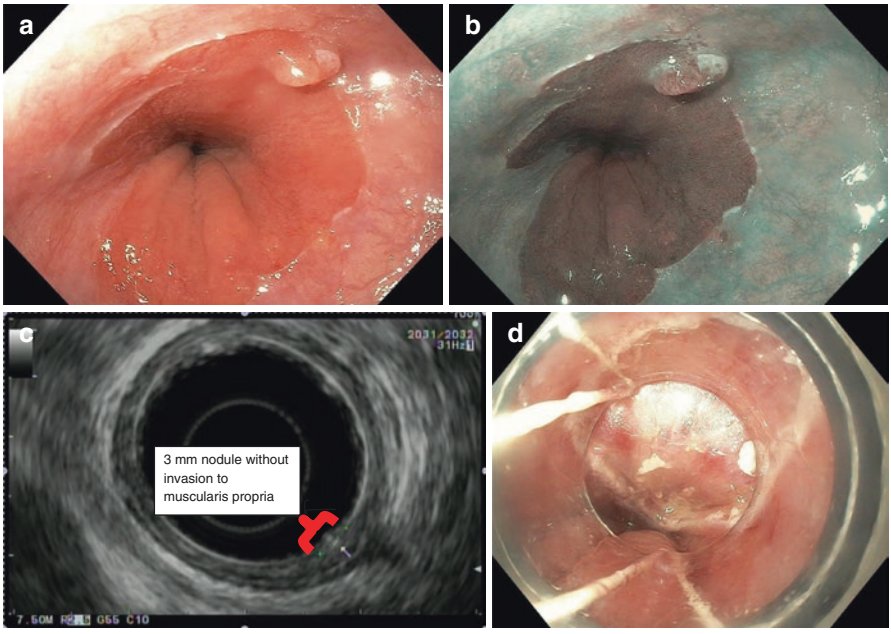

Fig. 8.1 Endoscopic staging of T1a esophageal adenocarcinoma. (**a**) 3 mm nodule at Z-line. (**b**) The same lesion visualized under narrow band imaging. (**c**) Endoscopic ultrasound showing the lesion limited to the mucosa. (**d**) Endoscopic mucosal resection (EMR) of the lesion. The pathology results revealed intramucosal adenocarcinoma with 4 mm negative margins. In this case the EMR was therapeutic as well as diagnostic

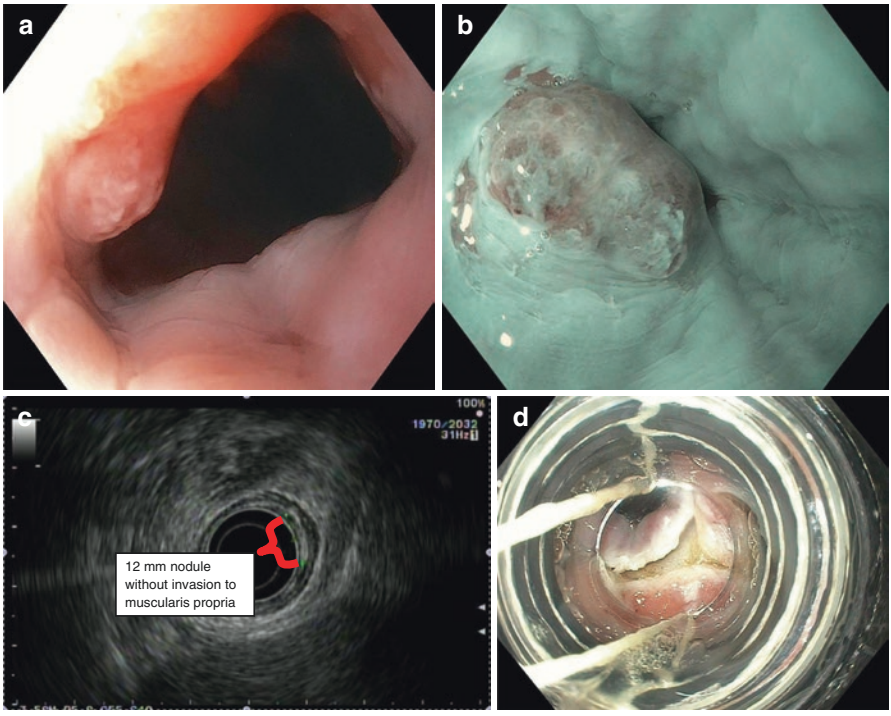

Fig. 8.2 Endoscopic staging of T1b esophageal adenocarcinoma. (**a**) 12 mm nodular mass at Z-line. (**b**) The same lesion visualized under narrow band imaging. (**c**) Endoscopic ultrasound showing the lesion not invading the muscularis propria. For this reason, endoscopic mucosal resection was indicated for staging. (**d**) Endoscopic mucosal resection of the lesion

tumors without malignant-appearing LNs [83]. Many studies show that when EUS is inaccurate it tends to overstage more often than understage, especially in superficial Barrett's neoplasms [84, 85]. In a study involving 125 patients with esophageal carcinoma (86% with adenocarcinoma), EUS was 80% sensitive for determining nodal metastasis compared to 40% for CT ($p < 0.001$). The diagnostic accuracy was 81% with EUS compared to 61% with CT ($p = <0.001$) [86].

Miniprobe EUS utilizes a slim catheter introduced via the working channel of an endoscope to provide high-resolution radial echoendosonographic images over a shorter depth of penetration. It can be used to examine the esophageal wall even in situations of stenosis. In a study involving 143 patients with esophageal carcinoma, 112 having EAC, 78% of patients were accurately staged and would have been assigned to the appropriate therapy group, while 11% were overstaged and would have been overtreated, and 11% were understaged and would have been undertreated using miniprobe EUS to differentiate locally advanced from limited cancer [87].

EUS is accurate in differentiating T1 and T2 lesions and superior to CT for lymph node staging according to a prospective trial with 100 patients with early Barrett's-related carcinoma [87]. The T-stage diagnosed with CT was T1 or less in every patient. Using EUS, the T-stage was T1 in 92% of cases and >T1 in 8%. Significantly more LNs were found with EUS compared to CT (28 vs. 19), and the

sensitivity of CT for N-staging was low compared with EUS (38% vs. 7%) [87]. In another study involving 48 patients with 8 having submucosal invasion, EUS provided accurate staging in 41/48 patients (85%) with only one patient overstaged and 6 patients understaged compared to the histologic diagnosis [88].

In another study involving 33 patients with adenocarcinoma, 21 with squamous cell carcinoma, and 1 with lymphoepithelial-like carcinoma, 86% of the 40 T1 m lesions on EUS were confirmed on pathology. Of the 33 T1sm lesions diagnosed on EUS, 66% were confirmed as T1sm. The accuracy of EUS in evaluation of LNM was 71% with negative predictive value of 84%. The accuracy by histological type was 70% for adenocarcinoma and 81% for squamous cell carcinoma, which was not found to be statistically significant [89].

Early detection of SCC is also very important as finding and treating these lesions can lead to a 5-year survival rate of more than 90% after endoscopic or surgical management [90]. EUS is considered to be the best option for staging esophageal SCC. A study showed that the accuracy of EUS for staging T1a lesions (mucosal lamina propria and muscularis mucosa infiltration) and T1b (submucosal infiltration) lesions was 70.8% (51/72) with a sensitivity of 74.3%. Multivariate analysis suggested that the accuracy of EUS was related to the length of the lesion ($p = 0.029$) [91].

A more recent study investigated the use of EUS and computed tomography-positron emission tomography (CT-PET) in relation to survival in esophageal cancer. In Kaplan-Meier analyses, patients who had EUS or EUS + CT-PET had improved survival for all stages compared with no EUS or CT-PET except in stage 0 disease. EUS increased the likelihood of receiving endoscopic therapies, esophagectomy, and chemoradiation. Multivariable Cox proportional hazards models demonstrated that receiving EUS was a predictor for improved 1-year (HR 0.49, 95% CI 0.39–0.59, $p < 0.0001$), 3-year (HR 0.57, 95% CI 0.48–0.66, $p < 0.0001$), and 5-year (HR 0.59, 95% CI 0.50–0.68) survival [92].

Endoscopic Treatment of Early Esophageal Cancer

Traditional therapy for early-stage esophageal cancer and BE with HGD had been esophagectomy with lymph node dissection. However, esophagectomy carries significant morbidity, ranging from 20 to 50% [93], and may have lifelong quality of life implications. In addition, the mortality from esophagectomy ranges from 2 to 9% [93–95]. Definitive endoscopic therapy with EMR of malignancy followed by subsequent RFA of residual BE has been increasingly utilized in BE with HGD as well as early-stage esophageal cancer, defined as Tis, T1a, and T1b tumors.

Endoscopic Mucosal Resection as Therapy for Intramucosal Adenocarcinoma

As discussed above, endoscopic mucosal resection (EMR) should be performed for diagnostic purposes in areas within BE with concerning features such as nodularity or mucosal irregularity. In these cases, it may provide diagnostic information (precise T-stage, degree of differentiation, margins, presence or absence of

lymphovascular invasion). The precise depth of tumor invasion may further refine treatment allocation. EMR may also be therapeutic in select cases of HGD, Tis, T1a, and certain T1b tumors, as it allows resection of the superficial layers from the submucosa (Fig. 8.1).

The efficacy and safety of endoscopic therapy with EMR in Tis and T1a lesions has been demonstrated [96]. Longer-term mortality outcomes for early-stage cancers have been similar between endoscopic therapy and esophagectomy [97–100]. Prospective studies have demonstrated complete oncologic eradication and low mortality with endoscopic therapy for Tis and T1a lesions [101–105]. The National Comprehensive Cancer Network (NCCN) recommends endoscopic resection of Tis and T1a esophageal adenocarcinoma followed by RFA as the preferred therapy. A recent study also demonstrated excellent outcomes with endoscopic therapy in highly selected cases with T1b adenocarcinoma limited to the superficial-most third of the submucosa (T1b sm1 lesions), though this approach continues to be debated [106].

Patient selection remains the critical question when deciding between endoscopic resection and esophagectomy for early-stage tumors. Since a decision to pursue endoscopic therapy over esophagectomy implies foregoing lymph node dissection, patient selection must be aimed at identifying patients at low risk for nodal metastasis. The risk of nodal metastasis and thereby the risk of incomplete oncologic outcome can be weighed against the risk of surgical mortality in selecting a treatment modality [5, 106].

A 2012 review of 70 studies and 1874 patients with surgical pathology showed no nodal metastasis in 524 patients with HGD and 26 of 1350 patients with intramucosal carcinoma, representing a 1.93% incidence of nodal metastasis in this group. More recently, an analysis of 715 patients with early-stage esophageal adenocarcinoma undergoing esophagectomy in the Surveillance, Epidemiology and End Results (SEER) database of the National Cancer Institute helped to stratify patients by risk of nodal metastasis according to tumor size and degree of differentiation. There were no cases of nodal metastasis among Tis cases. Among 323 T1a cases, 6.8% had nodal metastasis. The incidence was 5.2% among low-grade tumors, 2.3% among tumors smaller than 2 cm in diameter, and 1.7% among tumors that were both low grade and smaller than 2 cm. Among 353 T1b cases, 18.1% had nodal metastasis, with an incidence of 8.6% for low-grade tumors smaller than 2 cm and 3.0% for low-grade tumors smaller than 1 cm [107].

Other than depth of invasion, size, and histologic grade, lymphovascular invasion has been identified as a risk factor for nodal metastasis. Tumors with lymphovascular invasion are typically considered for esophagectomy due to the higher risk of nodal metastasis.

In a retrospective study involving 62 patients with superficial esophageal adenocarcinoma, there was a local recurrence in 14 of 64 patients, 3–36 months after EMR. Larger diameters were most commonly associated with recurrence ($p = 0.01$) [108]. Typically, a local recurrence is managed with repeat EMR. A prospective study of EMR in patients with either early esophageal adenocarcinoma or HGD in Barrett's esophagus showed promising results for use of EMR in lower risk disease. Complete local remission was achieved in 97% of a group of 35 patients with

"low-risk" disease, including macroscopic types I, IIa, IIB, IIc, lesion diameter up to 20 mm, mucosal lesion, histologic grades G1 and G2, and/or HGD. EMR may be a less invasive option for highly selected early cancers [96].

A study of 176 patients treated for mucosal EAC (T1a) with EMR or surgery had similar cumulative mortality (17%) with either method. Treatment modality was not a significant predictor of survival on multivariable analysis. Recurrent EAC was detected in 12% of patients treated endoscopically and all of the recurrences were successfully re-treated endoscopically [91]. In a study involving 114 patients with mucosal EAC treated surgically or endoscopically, complete remission (CR) was achieved in all patients except for one in the EMR group who died from other causes before CR could be achieved. Complications from surgery were found in 32% of patients with 0% major complications found in the EMR group ($p < 0.001$). There was a higher recurrence rate in patients who underwent EMR with one patient having local recurrence and four with metachronous neoplasia. Repeat endoscopic treatment was possible in all patients [109].

Another study involved the role of EMR in curing esophageal adenocarcinoma. The lesions had to meet low-risk criteria which included: lesion diameter <20 mm and macroscopically type I (polypoid), IIa (elevated), IIb (flat), or IIc (depressed) lesions that were <10 mm and well-differentiated or moderately differentiated adenocarcinoma (grade G1 (well differentiated)/G2 (moderately differentiated)) and lesions limited to mucosa (m type) without known nodal metastasis or lymphovascular invasion proven by histology. One hundred patients met these criteria and were treated with EMR. Results showed that complete local remission was achieved in 99 of 100 patients [103]. Median follow-up was 33 months, and during that time 11 patients developed metachronous lesions classified as high-grade dysplasia or mucosal cancer. After repeat endoscopic management all patients again achieved complete local remission. The authors calculated 1-, 2-, 3-, and 5-year survival rates as 99%, 99%, 98%, and 98%, respectively. No severe complications, such as bleeding or perforation occurred in the acute phase and no patients died. Common minor complications that occurred with EMR included hemorrhage after EMR successfully treated with epinephrine [103].

A study involving 107 patients with BE and suspected HGD or IMC had reassuring results for the eradication of neoplasia with EMR [110]. In 80.4% of patients, the BE was eradicated completely. Over the follow-up time of 40 months there was a 71.6% (53 of 74) complete remission rate from intestinal metaplasia and 100% complete remission rate from HGD (74 of 74) or cancer (74 of 74). HGD and IMC recurred in one patient each, and they were both treated to complete remission with EMR. Complications involved strictures in 41.1% and symptomatic dysphagia in 37.3% of patients requiring dilations. Perforations occurred in two patients after EMR and in one after dilation.

Some centers have reported good results with superficially invasive submucosal EAC treated endoscopically. One study showed no lymph node metastases in T1b sm1 lesions (tumor invasion limited to the superficial third of the submucosa) [111]. In another study of 120 patients with HGD or T1 adenocarcinoma, 1% showed LNM in T1m1–3/sm1 tumors compared with 44% of T1sm2 and 3 tumors [112].

EMR has also been used for small, localized esophageal squamous cell neoplasms as an alternative to surgical therapy. It has been shown to have similar efficacy when compared to esophagectomy [113]. EMR is limited by the size of the lesion due to the increased risk of piecemeal resection in larger lesions leading to more recurrence of disease and incorrect histological evaluation [114]. Endoscopic submucosal dissection (ESD) is common in Asia and allows removal of larger esophageal lesions en bloc. ESD may have a lower local recurrence rate than EMR [114–116].

Radiofrequency Ablation for Barrett's Esophagus with Dysplasia

The recommended management for BE with HGD without adenocarcinoma is EMR for any suspicious lesions followed by RFA [5]. In a landmark multicenter, sham-controlled trial, 127 patients with dysplastic BE underwent RFA or a sham procedure. Among patients with LGD, complete eradication occurred in 90.5% in the RFA group and 22.7% in the control group ($p < 0.001$). In the HGD group, there was an 81% eradication rate in the RFA group compared with 19% in the control group ($p < 0.001$). In the RFA group, 77.4% of patients had complete eradication of intestinal metaplasia compared with 2.3% in the control group ($p < 0.001$) [14]. Given the high rate of progression to adenocarcinoma typically observed among patients with HGD, this study established the utility of RFA for patients with HGD.

The use of RFA for LGD in BE is being evaluated. The rate of progression from LGD to adenocarcinoma is lower than in HGD. Reports of the use of RFA for treatment of low-grade dysplasia are heterogeneous with short follow-up periods as found in a meta-analysis of 37 studies and 521 patients with LGD [117]. Due to the lack of data on long-term follow up, the potential benefit of ablation in reducing carcinoma risk in those with LGD compared to the risks and cost of treatment with RFA is incompletely characterized [5, 118]. The American Society for Gastrointestinal Endoscopy (ASGE) recommended in 2011 that select patients with BE LGD be considered for ablation procedures [119]. In a study involving 68 patients with LGD randomized to RFA and 68 patients with LGD randomized to endoscopic surveillance, ablation reduced the risk of progression to HGD or adenocarcinoma by 25% (1.5% for ablation v. 26.5% for control, $p < 0.001$) [30]. The absolute risk of progression from LGD to adenocarcinoma was reduced by 7.4% ($p = 0.03$). Among patients receiving RFA, complete eradication occurred in 92.6% with dysplasia and 88.2% with intestinal metaplasia compared to 27.9% with dysplasia and 0% with intestinal metaplasia in the control group. Follow-up was over a 3-year period. In practice, due to the good safety profile of RFA and anxiety surrounding observational management for a premalignant lesion in the esophagus, RFA is frequently offered in the setting of LGD.

In 2013, a systematic review and meta-analysis of studies examined the rate of complete eradication of dysplasia and intestinal metaplasia and the rate of IMC recurrence after treatment. Complete eradication of metaplasia and dysplasia occurred in 78% and 91% of patients, respectively. IMC recurrence occurred in

13% of patients. Stage advancement to cancer occurred in 0.2% of patients during treatment and in 0.7% after complete eradication of metaplasia. Heterogeneity was a noted limitation [120].

A retrospective review involving 36 patients at two tertiary care facilities with biopsy-proven IMC were treated with RFA after or during treatment with EMR. Complete eradication of IMC/dysplasia was achieved in 89% with patients requiring a mean of 1–2 EMRs and 2–3 RFA sessions to achieve eradication. The mean follow-up period was 24 ± 19 months and complete eradication at that time was 81%. Treatment complications included bleeding in 3% and stricture formation in 19% [121].

HGD or carcinoma can develop in some patients even after previous successful eradication of neoplasia or intestinal metaplasia. There have been reports of patients developing subsquamous neoplasia at least 6 months after RFA and two patients who developed subsquamous neoplasia after EMR and before RFA. It is possible that anatomical characteristics could interfere with the energy delivery of RFA to lesions. While continued surveillance is indicated in patients who have undergone RFA, the proper intervals are unknown. One approach has been to perform surveillance endoscopy every 3 months for 1 year after ablation and then increase the interval to every 6 months for 1 year, subsequently increasing to annually [122]. EMR and RFA have been used in tandem to increase the rate of complete remission of Barrett's-related lesions. However, using RFA after EMR may increase the risk of complications such as esophageal scarring. This can lead to increased risk of tears, strictures, and perforations. However, several studies have shown that these risks are low and may be equal to using RFA alone [34, 123, 124].

A more recent study involving a large, multicenter registry investigated the safety and efficacy of RFA vs. RFA after preceding EMR for nodular BE with advanced neoplasia (HGD or IMC). Safety outcomes included stricture, bleeding, and hospitalization while efficacy outcomes included complete eradication of intestinal metaplasia (CEIM), complete eradication of dysplasia (CED), and number of RFA treatments needed to achieve CEIM. CEIM was achieved in 84% of patients treated with RFA alone or after EMR. CED was achieved in 94% of patients with combination therapy and 92% with RFA only ($p = 0.17$). Safety outcomes and durability of eradication were not different between groups [125].

Another study comparing RFA in BE with HGD and IMC using a UK registry showed that in 515 patients, those with IMC were more likely to have visible lesions requiring preceding EMR than those with HGD and these may carry a higher risk of cancer progression. Patients underwent RFA every 3 months until all visible BE mucosa was ablated or cancer developed. The 12-month complete response for dysplasia and IM were almost identical ($p = 0.7$) and progression to invasive cancer was not significantly different at 12 months ($p = 0.19$). In IMC, RFA with preceding EMR was associated with superior durability compared with RFA alone ($p = 0.01$) [32]. A 6-year follow-up study looking at 508 patients completing therapy with combined EMR and RFA for BE-related neoplasia showed that complete remission of dysplasia (CR-D) and complete remission of intestinal metaplasia (CR-IM) improved significantly from 77% and 56% to 92% and 83%, respectively

($p < 0.0001$). EMR for visible lesions before RFA increased from 48% to 60% ($p = 0.013$). Rescue EMR after RFA decreased from 13% to 2% ($p < 0.0001$). No difference was seen to be significant in terms of progression to OAC at 12 months ($p = 0.51$) [29].

The EURO-II study involved 13 European centers and looked at EMR followed by RFA to eradicate BE with HGD and/or IMC. There were 132 patients undergoing a median 3 RFA treatments with complete eradication of neoplasia achieved in 92% and CE-IM in 87%, per intention to treat analysis, and 98% and 93%, respectively, in the per-protocol analysis. Mild-to-moderate adverse events occurred in 19% of patients. This study showed that intensive multimodality endotherapy with EMR and RFA is safe and highly effective [31].

Conclusions

The incidence of esophageal adenocarcinoma is progressively increasing and its growth rate outpaces that of the other major epithelial malignancies. Endoscopy has a critical role in the evaluation, diagnosis, staging, and management of Barrett's esophagus and esophageal cancer. Screening may be considered for patients with GERD, especially in the presence of any red-flag symptoms such as weight loss, dysphagia, or bleeding. Surveillance is utilized in patients with Barrett's esophagus to detect progression to dysplasia and early cancer, when tumors are superficial and curable by endoscopic or surgical modalities. Endoscopic ultrasound is the modality of choice for the locoregional evaluation of esophageal tumors, establishing the T and the N stage. EMR provides very specific diagnostic and staging information with early tumors, further refining considerations for treatment allocation. EMR forms the cornerstone of endoscopic treatment for early cancers. EMR is also indicated for any nodularity or mucosal irregularity in patients with dysplasia. Radiofrequency ablation is the treatment of choice for flat Barrett's esophagus with high-grade dysplasia, and following EMR once all the nodularity has been resected. As technology continues to progress, endoscopic approaches stand to provide ever-greater detection, more accurate staging, and less invasive management options for the large population of patients with esophageal cancer.

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