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Clinical endoscopic management of early adenocarcinoma and squamous cell carcinoma of the esophagus (screening, diagnosis and therapy)

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Abstract

Since the esophagus is easily accessible with endoscopy, early diagnosis and curative treatment of esophageal cancer is possible. However, diagnosis is often delayed because symptoms are non-specific in the early stages and the onset of dysphagia is associated with advanced disease, which has a 5-year survival of less of 15%. Mass screening by endoscopy is not cost-effective, hence a number of alternative imaging and cell sampling technologies are under investigation. The ideal screening test needs to be inexpensive, well tolerated and applicable to primary care. Over the last 10 years, significant progress has been made in the endoscopic diagnosis and treatment of dysplasia (squamous and Barrett's) and early esophageal cancer using resection and ablation technologies supported by evidence from randomised controlled trials. Here we review the state-of-the-art technologies for early diagnosis and minimally invasive treatment, which together have the potential to reduce the burden of disease.

Keywords

Barrett's esophagus; esophageal cancer; screening; endoscopy

Screening

Rationale and criteria for screening

Screening refers to a programme in which individuals are invited by a health care professional or system to undergo a test for a medical condition. The target may be the general population often enriched to some extent, for example by age or sex, to increase the prevalence of the disorder in those tested. Alternatively, systematic testing might target a symptomatic group of individuals, who might not otherwise have been investigated. In the context of esophageal cancer, screening would aim to detect Barrett's Esophagus (BE) and dysplasia in squamous epithelium, which are precursor lesions to esophageal adenocarcinoma (EA) and esophageal squamous cell carcinoma (ESCC), respectively. In order to fulfil the updated Junger criteria 1 for screening any testing would need to be conducted in an enriched population in view of the low prevalence of the disease and the low conversion rate. The target population can be defined according to known risk factors for BE and squamous cell dysplasia, which have high geographical variation (see article by Abnet et

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al in this Special Issue) 2. However, given the high prevalence of some risk factors, for example reflux in the context of BE, and the need for confirmatory investigations to reach a definitive diagnosis, it is essential that the screening test has a high specificity to reduce the number of false positives and the burden of un-necessary invasive procedures. The characteristics of different screening tests for esophageal cancer are summarized in table 1.

Conventional endoscopy

Esophago-gastro duodenoscopy (EGD) is the gold standard test for esophageal cancer and the precursor lesions. For patients who consult their General Practitioner with upper gastro-intestinal symptoms, it has been shown that the referral rates for endoscopy vary significantly from practice to practice and this is likely to be the case worldwide depending on the level of awareness and nature of the reimbursement systems for endoscopic procedures 3, 4. Furthermore, since there is effective medication available over the counter to relieve gastro-esophageal reflux symptoms most individuals will not seek medical advice 5.

In one region of exceptionally high ESCC incidence in China, endoscopic screening is performed for asymptomatic adults using a mobile van to reach rural areas. Lugol's iodine is sprayed at endoscopy to identify non-staining areas more likely to harbor dysplasia (Figure 1F), which can be treated endoscopically. This strategy has proven effective in reducing the incidence and mortality from ESCC 6. The optimal stratification criteria to increase efficiency of these programs are not yet clearly defined.

In individuals referred for investigation of gastro-esophageal reflux symptoms most society guidelines recommend endoscopy and biopsy in case of endoscopically visible BE 7–10. However, screening for BE is only recommended for patients with multiple risk factors (age older than 50, white race, male sex, chronic reflux symptoms, obesity), 7, 8. The British Society of Gastroenterology guidelines suggest that the threshold for screening should be lowered when there is a family history of esophageal adenocarcinoma (EA).

Overall mass endoscopic screening to detect and remove dysplastic lesions in squamous esophageal epithelium or BE would present a substantial challenge even in a high-resource environment and is not tenable even in high incidence regions.

Office-based trans-nasal endoscopy

Trans-nasal endoscopy (TNE) is better tolerated than EGD, since small caliber endoscopes (<6 mm) inserted transnasally do not touch the root of the tongue, which reduces the gagging reflex and dispenses the need of sedation. Novel disposable and more compact designs are compatible with office-based practice or mobile units 11, 12.

In the context of screening for squamous cell carcinoma unsedated TNE has been shown to be safe and feasible with similar detection rates compared with Lugol's chromoendoscopy in some series enriched for patients at high risk13 14.

Currently the American College of Gastroenterology is the only society that suggests the use of unsedated TNE for patients undergoing screening for BE 7. Three randomized, cross-over

studies of TNE in reflux populations enriched with known BE cases demonstrated a sensitivity for detecting BE of 84- 98% 15, 16. However, due to the small TNE biopsy forceps there is a lower sensitivity (66.7%) for histologic diagnosis.

A recent meta-analysis showed that unsedated TNE is preferred to conventional endoscopy in 63% of cases (95% CI, 49.0-76.0, 10 studies) and has high acceptability rates 11. However, a community-based randomised controlled trial on over 400 individuals failed to show higher participation rates for TNE in a mobile unit than standard endoscopy in a hospital outpatient unit 15.

However, physicians may be reluctant to use TNE when it requires very similar time and expertise to conventional endoscopy, with the intrinsic caveats of small biopsy size and reduced field of view17, 18. Furthermore, the cost of ultrathin devices may not allow wide-spread distribution in primary care. Large community-based cohort studies are required to assess fully the suitability of TNE for esophageal cancer screening.

Imaging via capsule endoscopy

Imaging capsules have generally been tested in the context of BE, but not squamous cell dysplasia. The majority of studies have been carried out using untethered dual-camera wireless capsule endoscope19, however to obviate to rapid esophageal transit tethered cameras have been developed. A meta-analysis of nine studies (618 patients) showed a pooled sensitivity of 77%, ranging from 73 to 90%, depending on whether the histologic or endoscopic diagnosis were used as gold standard, respectively 20. However two studies in an un-enriched screening population reported sensitivities of 60% and 78% respectively21, 22. Further large-scale studies in the relevant population are required to assess its suitability for screening, but, despite the high levels of safety and acceptability, the cost might make this prohibitive23.

Volumetric laser endomicroscopy

Volumetric laser endomicroscopy (VLE) is a new generation optical coherence tomography, which produces high-resolution, three-dimensional cross-sectional images of the esophagus. VLE has also been produced as a tethered capsule endomicroscopy. In a proof of principle study tethered VLE could distinguish between patients with and without BE and subsequently an automated segmentation and characterization algorithm has been developed to make this technology more clinically applicable24, 25. Once the capsule is withdrawn it can be disinfected for reuse, making it potentially inexpensive and feasible to be used for population screening.

Similarly to capsule endoscopy the question remains whether an optical diagnosis can suffice without a tissue sample given that identification of cellular atypia is critical to inform patient management.

Esophageal cell collection devices

Over many years, investigators have explored the use of esophageal cell collection devices, which can be deployed via a catheter or swallowed by the patient26–31. Unfortunately, the

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accuracy was too low to be clinically useful due to a low cell yield and the reliance on standard cytology to diagnose cell atypia.

Recently an encapsulated sponge device (Cytosponge™), which can sample the entire esophagus has been more effective due to the high cellularity. There is now evidence that Cytosponge™ is an accurate screening tests for BE32, 33 and early data suggests that this approach may prove useful for primary detection of squamous dysplasia as well 34.

Diagnosis of BE on Cytosponge™ material is achieved with an immunohistochemical assay for a biomarker called TFF3, which is highly specific for IM31. The sensitivity of Cytosponge™ for BE varied between 73.3% (95% CI, 44.9% to 92.2%) in a primary care-based study of 500 patients and 79.9% (95% CI 76.4% to 83.0%) in a secondary care case-control study of >1,000 patients, with specificity ranging between 92 and 94% 32, 33,. In addition, the Cytosponge™ has high levels of acceptability, with 82% of participants reporting low levels of anxiety before the test and is generally preferred to conventional endoscopy ($p<0.001$)32, 33, 35. Finally, cytology samples can be subjected to additional molecular tests, such as DNA methylation assays and DNA sequencing, to refine diagnostic accuracy and allow risk stratification 36, 37.

A microsimulation study compared the cost effectiveness of BE screening by either Cytosponge™ or endoscopy vs no systematic diagnostic test and suggested that the Cytosponge™ test was cost-effective when combined with endoscopic therapy38. A further microsimulation study demonstrated that Cytosponge™ screening followed by endoscopic confirmation is a cost-effective strategy with ICER ranging from $28,791 to $33,307 39. A large primary care study of over 9,000 individuals (Trial ID ISRCTN68382401) is now underway to provide definitive evidence that screening with Cytosponge™-TFF3 test for patients with reflux symptoms increases the detection of BE in primary care.

Circulating molecular markers

A blood-based test would be an ideal screening platform to be carried out in a primary care setting. Five peptides have been identified in blood that could distinguish patients with ESCC from healthy volunteers and the peptide panel has been validated in an independent cohort40. A number of studies have shown that miRNAs can distinguish between BE patients and control individuals (including those with esophagitis) 41 but further work is required to validate these in a larger population. CtDNA can be detected at high allele fraction in cases with advanced esophageal cancer however the sensitivity in the context of early disease is not yet known 42. Synchronous cancers can affect the specificity of circulating markers and this will also need to be addressed in future studies. Some of these markers can also be applied to stool but the sensitivity for early lesions is unknown and any positive results would have to be followed up by evaluation of the entire GI tract unless the biomarker is highly specific for esophageal cancer43–46. Further work is needed in this area given that few of these tests have been investigated in the context of screening.

Volatiles detected in breath

Biomarkers detected in a breath sample are an attractive method for cancer screening since it is non-invasive, applicable to the primary care setting and is likely to be cost-effective. One

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study identified a panel of breath volatile organic compounds (VOC) that could be used to distinguish esophago-gastric cancer from non-cancer controls with an area under the ROC curve (AUC) of 0.87 in the validation set, however its performance to diagnose BE is still unclear 47. Another study used an e-nose device to differentiate VOC from BE patients vs control individuals with an AUC of 0.79 48. These results are promising but need further validation in a screening setting.

Endoscopic Diagnosis

Conventional white light endoscopy

Endoscopic diagnosis of early esophageal cancer refers to the detection of early malignant lesions, which are curable and associated with a high survival rate and pre-invasive neoplasia, also known as dysplasia. BE-related dysplasia is often inconspicuous, therefore, the mainstay of endoscopic surveillance for BE remains random sampling according to the Seattle protocol (quadrantic biopsies every 1 or 2cm) 7, 8, 49. This protocol has several disadvantages, including sampling error, long-procedural time, poor patient tolerability and high costs, leading to low adherence in clinical practice (<50%) 50. Factors that relate to higher neoplasia detection are the inspection time and the use of high-resolution endoscopes, which in a RCT had equal accuracy for dysplasia compared to chromoendoscopy 51, 52.

Similarly, squamous dysplasia, the precursor lesion to SCC, has a very subtle appearance on WLE (Figure 1 E). In a screening setting in high-risk individuals, at least 40% of early SCC were missed by conventional WLE 53. In a community setting study in high-risk geographic areas the sensitivity of WLE targeted biopsies for squamous dysplasia was 7.7% 54. Unlike BE, random sampling in SCC screening has not been optimized as the entire esophageal mucosa can harbour pre-cancerous lesions and extensive esophageal sampling would be impractical.

Several endoscopic techniques to improve dysplasia detection with minimal biopsy sampling have been investigated, which are summarized in Table 2.

Chromoendoscopy

Methylene blue and indigo carmine chromoendoscopy have been extensively investigated. A meta-analysis of 9 studies showed no incremental diagnostic yield by methylene blue-targeted biopsies for the diagnosis of dysplasia 55. Similarly, a randomized cross-over study found that indigo carmine chromoendoscopy did not increase the dysplasia detection rate compared to high-resolution WLE 52. More recently, promising results in the BE field have been obtained with acetic acid (AA) chromoendoscopy. Topical application of 1.5-2.5% AA stains non-dysplastic BE mucosa in white, while early neoplasia loses the whitening effect (loss of acetowhitening) within few seconds (Figure 1A-B). A single-center retrospective study has investigated the differential diagnostic yield between AA-targeted biopsies and Seattle protocol in two cohorts of patients endoscoped by different endoscopists 56. The overall dysplastic yield in the AA group was 6-fold higher than the Seattle protocol group (12.5% vs 2%, p=0.0001), with significantly fewer biopsies needed. Two recent meta-analysis showed high diagnostic accuracy for HGD/intramucosal cancer (IMC) (Table 2)57,

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58. Moreover, AA improves definition of the mucosal pit for prediction of histology with irregular/distorted pit being suggestive of HGD (Figure 1 C-D). However, more research is warranted to evaluate whether AA chromoendoscopy allows dispensing random biopsies.

Lugol's iodine chromoendoscopy (LCE) is a useful adjunct to diagnose occult squamous cell neoplasia in high-risk individuals as flat squamous neoplasia appears as a Lugol-voiding lesion (LVL) (Figure 1 E-F). In a cohort of 190 high-risk subjects (heavy smokers and drinkers), LCE-targeted biopsies showed a sensitivity of 46%, a specificity of 90% for squamous HGD 59. In a large cohort study over 60% of LVL larger than 10mm had at least HGD (HR for neoplasia 5.9 (CI 1.3–42.8)), whereas less than 4% of LVL <5mm showed HGD 60. Pink discolouration of the LVL within 3 minutes from the staining (pink sign) significantly correlates with at least HGD on histology61.

Electronic chromoendoscopy

Electronic chromoendoscopy allows colorimetric manipulation of endoscopic images by a button-switch. Digital image processing techniques, such as i-scan and Flexible spectral imaging color enhancement (FICE), enhance images acquired on WLE, whereas light filter technologies, such as narrow band imaging (NBI) and autofluorescence imaging (AFI), employ specific wavelengths to image tissue. More recently, blue laser imaging (BLI) has been become available, which utilizes two monochromatic lasers at 410nm and 450nm. The small number of studies on i-scan, BLI and FICE does not allow to draw conclusions on their usefulness in dysplasia detection.

NBI has been largely investigated in the BE field. In a cross-over trial on 123 patients comparing WLE with targeted and random biopsies with non-magnified NBI with targeted biopsies only, NBI detected a higher proportion of dysplastic lesions than WLE (30% vs 21%, p=0.01), with significantly fewer biopsies (3.6 vs 7.6, p<0.0001), 62. However, the per-patient analysis failed to show significant difference in the proportion of patients diagnosed with dysplasia. Two meta-analyses showed an overall sensitivity and specificity for HGD/IMC ranging between 91 and 94.2%, and 85 and 94.4%, respectively 58, 63. Magnified NBI allows histology prediction, based on the enhancement of the superficial mucosa, and the identification of the demarcation line of early neoplasia to inform endoscopic resection (Figure 1 K-L). A binary classification of pit and vasculature in regular/irregular has a sensitivity and specificity for HGD of 80.4 and 88.4%, respectively64.

Early SCC appears on NBI as brownish discoloration of the esophageal mucosa (Figure 1 G). In a high-risk cohort of 202 patients non-magnified NBI showed similar sensitivity to LCE, but significantly higher specificity (75%, vs 64%, p=0.01) 65. Magnified NBI allows prediction of histology by characterization of shape, calibre and directionality of the micro-vessels penetrating the mucosal layer, also called intra-papillary capillary loops (IPCL) (Figure 1 H) 66, 67. Recently, Goda and co-workers randomized 303 high-risk patients to either magnified NBI or LCE with assessment of pink-sign. The overall accuracy of NBI and LCE for HGD or invasive SCC was similar (91.2% and 90.5% respectively); however, NBI was significantly faster 68. A meta-analysis comparing NBI and LCE showed equivalent

sensitivity for early SCC, but higher specificity for NBI, which allowed better distinction between neoplastic lesions and benign mucosal alternations 69.

AFI exploits different fluorescence properties of normal and neoplastic esophageal mucosa by utilizing a blue light (395-475nm) to excite endogenous fluorophores to emit green fluorescence. In the context of SCC, NBI and LCE have better image quality and allow better delineation of the lesions compared with AFI 70, 71. Larger prospective studies have been performed in the field of BE-related neoplasia. Curvers and collaborators conducted two prospective studies with slightly contrasting results. In a first cross-sectional prospective study, the yield of neoplasia in the AFI-targeted biopsies was significantly higher than WLE-targeted + random biopsies 72. However in a follow-up cross-over study, AFI with targeted biopsies and standard WLE with targeted and random biopsies had equal accuracy for neoplasia in the per-patient analysis 73. The ASGE technology committee meta-analysis found a sensitivity and specificity for BE-related neoplasia diagnosis of only 80% and 46%, respectively. Overall, routine use of AFI is not recommended, but it may be useful to further direct lesion delineation prior to endoscopic resection (Figure 1 I-J).

Confocal laser endomicroscopy (CLE)

CLE allows direct microscopic analysis of the mucosa at the cellular and glandular architectural level. There are two CLE systems, the probe-based CLE (pCLE) and the endoscopy-integrated CLE (eCLE). pCLE is inserted through the standard 2.8mm working channel of commercial endoscopes and has a lateral resolution of 1 μm and a fixed imaging depth of 55-65 μm. In non-dysplastic BE, CLE demonstrates regularly shaped columnar cells, goblet cells and glands with regular contours and interglandular space (Figure 1 M); HGD is associated to darker glands with irregular shape and margins, loss of goblet cells and cellular pleomorphism (Figure 1N) 74. In a cross-sectional study on 101 patients with BE, the combination of pCLE had sensitivity and specificity for HGD/intramucosal cancer (IMC) of 93.5% and 67.1%, respectively. The ASGE meta-analysis found pooled sensitivity and specificity for HGD of 90.3% and 77.3%, respectively 58. The eCLE system has a higher spatial resolution of 0.7 μm and a variable depth of penetration. In a randomized study on 192 patients with BE, eCLE had an overall 95% sensitivity for HGD/IMC reducing by 2.7-fold the total number of biopsies required75. A disadvantage of CLE is the narrow field of view that can lead to sampling error. This can be circumvented using CLE in combination with wide-field flagging techniques (Figure 1 O-P). In a single center cohort study, AFI was used to direct pCLE, which achieved together a sensitivity and specificity for BE-related dysplasia of 96.4% and 74.1%, respectively 76. Similarly, flagging techniques such as i-scan and LCE have been used to direct CLE to diagnose squamous dysplasia. 77 78 79 Despite the cellular resolution, CLE has a limited application in clinical practice for several reasons including costs of the technology, the restricted availability in some geographical areas and the lack of consensus for some diagnoses such as early squamous neoplasia.

Novel technologies

New diagnostic techniques are emerging based on innovative imaging algorithms. Volumetric laser endomicroscopy (VLE) has been integrated in a 6cm balloon-based

catheter, which allow fast cross-sectional imaging of long segments of BE, with a axial resolution of 7 μm and a depth of penetration of 3mm. VLE diagnostic criteria for diagnosis of squamous esophagus, non-dysplastic BE and BE with HGD have been developed ex-vivo and validated on images obtained during in vivo procedures with high overall interobserver agreement (κ value= 0.81) 80. In a small cohort study of 6 patients, VLE helped identify BE-associated neoplasia, which was inconspicuous on WLE and NBI 81. However, detection of LGD with VLE remains unexplored.

Raman spectroscopy quantifies the energy shifts between incident and scattered light. With an endoscopy probe Bergholt and colleagues were able to diagnose HGD in a cohort of 77 patients with an area under the ROC of 0.90 82. An endoscopy probe has also been developed to examine the shape of elastic back-scattering of polarized light in early BE neoplasia 83. Implementation of spectroscopic techniques into user-friendly endoscopy devices has been challenging and more translational research is required.

In molecular imaging Injected or topically applied fluorescent probes allow detecting specific biological events. By phage display Sturm and co-workers identified a peptide (ASY) with high affinity for oesophageal cancer cell lines, which could be detected *in-vivo* by pCLE in areas of early BE-neoplasia 84. As an approach with a wide field of view a lectin called WGA, which is differentially bound in dysplasia, was used in *ex-vivo* whole esophageal imaging in combination with an AFI endoscope to identify neoplastic areas based on their low fluorescence intensity 85. Recently, in a mouse model of SCC an antibody against periostin, an integrin-binding protein important in tumor development, was used in conjunction with NIR to image SCC in murine esophagus. 86

Molecular diagnosis can be obtained on biopsy samples directed by advanced imaging. For example, a 3-biomaker panel tested on AFI positive areas achieved a 96% sensitivity for HGD/IMC with a 4.5 fold reduction in the number of biopsies required 87.

Endoscopic Therapy

Resection Techniques

Endoscopic therapy is now the treatment of choice for esophageal mucosal neoplasia88, with comparable long term overall and cancer-specific survival to surgery 89. Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) allow at the same time therapeutic resection and precise cancer staging. Careful delineation by high resolution WLE and /or advanced imaging is required prior to EMR/ESD and lesion description according to the Paris classification90 is recommended. Curative EMR is associated with lesions with Paris types I (polypoid), IIa (slightly elevated), IIb (flat), and IIc (slightly depressed), lesion < 20 mm, histological grades G1 and G2 and/or high-grade dysplasia in biopsy. Excavated lesions, those biopsied with poorly or undifferentiated cancer, suspected deep submucosal invasion, or associated malignant lymphadenopathy by EUS are better managed with surgery or chemo-radiation therapy according to the fitness and patient preference.

Technical aspects of EMR and ESD

There are various EMR techniques. The technique based on lifting by fluid injection followed by direct snare excision is rarely performed in the esophagus and should be restricted to pedunculated or semi-pedunculated lesions, which are very uncommon in the esophagus. Cap-assisted techniques are the preferred options in most cases. The “suck-and-cut” method (originally described by Inoue) is based on suction of the lesion lifted by saline injection within a transparent cap (Olympus, Japan), where a snare is pre-opened at the distal edge 91 92. Alternatively, EMR may be efficiently performed using a cap similar the variceal band ligator (Cook Medical, IN USA) without prior submucosal injection (“multiband” EMR, originally described by Soehendra92) (Figure 2A). The mean depth of specimens from different EMR techniques is about 5 mm, including substantial submucosa, with no significant differences by technique91. Indeed, about one half EMR specimens have muscularis propria at the deep margin91, which supports the use of the term “endoscopic resection” over “endoscopic mucosal resection”. Extensive nodular BE or larger lesions can be treated by multiple resections. Complete endoscopic resection of limited BE lengths (< 5 cm) can be successfully achieved (stepwise radical endoscopic resection, or SRER).

The typical ESD technique involves delineation of the lateral borders with a safety margin of at least 2 mm using coagulation markers. Injection of fluid (typically saline, epinephrine, and a dye like indigo carmine, or hyaluronic acid) underneath the target lesion is then followed by circumferential cutting, dissection of submucosal tissues, coagulation of visible vessels, and removal of the ESD specimen *en-bloc*. Endoscopic assessment of the ESD site for completeness of resection (including coagulation markers), bleeding, and perforation is essential. Histologic evaluation of the EMR/ESD specimens includes determination of tumor-free margins or R0 resection, lymph-vascular invasion (LVI), and tumor differentiation. The tumor depth of invasion affects tumor management and survival93. Early EAs that invade into the mucosa (T1a) are associated with a very low risk for lymph node metastasis (typically <2%) and endoscopic therapy could be completely curative94. There is emerging evidence that EAs with superficial sub-mucosal invasion (T1b-sm1, < 500 microns), well differentiated and with no LVI have also small risk of lymph-node spread (good prognosis T1b) and could be managed endoscopically 95–97. In contrast, the risk of lymph-nodal metastasis in T1a m3 and T1b sm1 SCC i is significantly higher. Hence, this sub-group has only a relative indication for endoscopic therapy in selected cases98.

Efficacy of EMR and ESD according to the type of Neoplasia

EMR of selected early ECA leads to very high cure rate (97-98%) and 5-year survival rate of about 98%, comparable to surgery, with treatable metachronous recurrences99, 100. Complete ER or SRER leads to very high eradication rates of 95-100% in patients with BE neoplasia with an average BE length of 2-4 cm101. Larger lesions that are longer than 5 cm or involving >75% of the esophageal circumference are best treated with EMR or ESD followed by ablation for residual BE 102. The combination of resection plus ablation leads to high eradication rates (Tables 3). The best long-term treatment outcomes are achieved after complete eradication of all neoplastic lesions and BE. Incomplete eradication all BE leads to metachronous neoplasia in approximately 15% of cases 103. ESD is widely performed in Asian Countries and emerging in Western countries104 105. ESD has been

studied as a resection technique to achieve *en-bloc* resection of BE-related neoplastic lesions, particularly with lesions > 15 mm, poorly lifting lesions, and lesions at risk for submucosal invasion106–108. However, it has not been proven to be superior to EMR for excision of mucosal BE cancer and EMR is preferred 109. Furthermore, ESD median procedure time is considerably longer (75-121 minutes) than for multiband EMR (25-30 minutes).

Although there is evidence that EMR is safe and effective for ESCC110, a large retrospective series showed that ESD associated to higher R0 resection rate than EMR (100 vs 53%, $p<0.05$) and lower local recurrence rate (0.9 vs 9.8%; $p<0.05$) 111. For early ESCC in Asia, ESD can lead to remarkable long-term cure, with 5-year overall and disease-specific survival rates of 90-99%, and 100%, respectively, in patients treated at expert centers 112, 113. Similar disease-specific survival for ESCC after ESD was reported in a European study 105. The cumulative incidence rate of metachronous tumors 5 years after ESD was 16.8%113, underscoring the need for long-term surveillance. For early ESCC, ESD is considered the technique of choice by European but not American guidelines114, 115.

Safety of EMR and ESD

Endoscopic resection is safe when performed by highly experienced endoscopists. The main adverse effects are bleeding and stricture formation. For ESD, bleeding occurs in 0.9-6.7% of BE cases 104–108. For extensive EMR or SRER, bleeding ranged widely between 2.4% and 25%101, 116. Perforation rate after ESD and EMR is low (0-5%) and can be treated with clips, stenting, or conservative management101, 103, 104, 106, 108. Complete excision of BE by SRER technique can lead to high stricture rates (33-88%) even in selected patients with limited BE length < 5 cm and lower risk Paris lesions 101, 117. Similarly, stricture is common ESD for BE neoplasia (15-60%)107, 108. These can be difficult to manage. The median number of dilations required for post-SRER and -ESD strictures are comparably high, about 3-4101, 104, 106, 108, 118.

Ablation Techniques

Unlike endoscopic resection techniques, ablative treatments involve thermal injury through heat (burning, coagulation necrosis), or freezing (cryotherapy) to destroy, rather than remove, neoplastic tissue. For BE healing of injured mucosa and replacement by neo-squamous tissue follows ablation if acid reflux is well-controlled. Ablation of esophageal neoplasia is typically performed on flat or non-nodular mucosa or following EMR or ESD of mucosal lesions after the resection site has healed (approximately 4-12 weeks later). Pathologic staging should confirm the absence of residual cancer at the deep and lateral margins of the specimen. Table 3 summarizes the 3 ablation techniques currently used for treatment of BE neoplasia. Some studies reported ablation outcomes for flat BE without EMR 119, 120, while others provided results of combined EMR plus ablation in dysplastic BE and early EA121–128.

Argon Plasma Coagulation (APC) for Barrett's Neoplasia

APC is a widely available focal thermal non-contact ablation technique involving transmission of current through argon gas, resulting in immediate coagulation necrosis

(Figure2B). It is commonly performed for treatment of small residual or recurrent areas of flat BE following EMR, ESD, or RFA. A pilot study using hybrid-APC (50 watts, Erbejet2, Germany) for primary eradication of non-dysplastic BE after EMR for IMC or HGD reported a median of 3.5 procedures to achieve complete eradication of IM (CE-IM) 39/50 patients (78%)125 (Table 3).

Radiofrequency Ablation (RFA) for Barrett's Neoplasia

RFA is the ablation modality with the largest body of evidence and considered the technique of choice by several national and international societies 8, 10, 121. RFA efficiently delivers heat energy to the mucosa in contact with the electrodes on disposable catheters (Barrx, Medtronic, Ireland) and a thermal burn is immediately visualized (Figure 2C). Treatments are repeated every 10-12 weeks until all BE is eliminated in a median of 2-3 sessions. A substantial amount of high and moderate quality evidence supports RFA as the best endoscopic ablative technique for clinical use (Table 3). A meta-analysis of 18 studies (3802 patients) treated with RFA showed a one-year rate for complete eradication of dysplasia (CE-D) and CE-IM of 91% (95% CI 87-95%) and 78% (95% CI 70-86%), respectively 129. Importantly, RFA can significantly reduce the risk of progression of LGD and HGD to EA 119, 120. It is the only endoscopic eradication therapy that has been shown to lower the incidence of ECA (2%) and mortality (0.2%), with the greatest absolute benefit observed in patients with HGD130. The durability of RFA treatment is also high, with CE-IM rates of 85-90% at 4-5 years121, 131. However, recurrence of IM after successful RFA is not uncommon, ranging between 13% and 33%129. Recurrences are usually located in the distal esophagus or at the GE junction just distal to the neo-Z line and are successfully treated121, 124, 129, 132, hence even patients that achieve CE-IM are generally recommended lifelong surveillance.

Serious adverse events are rare following RFA. Overall, strictures develop in 5% (3-7% 95% CI) of patients, but can be as high as 14%116, 129. Bleeding is uncommon after RFA (1%, 95% CI 1-2%), but may be associated with aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs) or anticoagulation therapy 116, 126, 133. Several study showed that focal EMR prior to radiofrequency ablation (RFA) does not to increase significantly the adverse event rate and stricture rate (4.6% for EMR + RFA versus 7.7% for RFA alone); however a recent meta-analysis suggested there could be a two fold increase in the risk of stricture formation in patients who received prior EMR 134–137.

Radiofrequency Ablation for ESCN and ESCC

RFA has been the most studied ablative therapy for treatment of early ESCN. It can be applied to flat, large (≥ 3 cm, < 12 cm total length) non-invasive ESCN (MGIN, HGD), or used in combination with EMR or ESD for early ESCC. A UK registry study comprising 8 centers reported complete eradication of squamous neoplasia by RFA (in combination with EMR) of 50% at 12 months, with a median of 1 RFA session (range 1-3) 138. However, the stricture rate was 20% and 30% progressed to invasive cancer at 1 year. Two non-randomized clinical trials in China using circumferential RFA showed complete eradication of neoplasia in 84% and 97% of cases at 1 year139, 140. Post-RFA stricture rates varied from 13.8% to 21%, which higher than those reported for RFA for BE neoplasia. Overall

studies on RFA for flat ESCC show variable outcomes probably due to the higher risk of under-staging in squamous neoplasia compared to BE, based on the endoscopic appearance only. This suggests that in the context of this disease tissue resection modalities are still preferred to ablation techniques and RFA should not be routinely performed outside research trials.

Cryotherapy: Techniques, Efficacy and Safety

Cryotherapy or cryoablation involves freezing to destroy unwanted tissues *in situ*. Unlike APC or RFA, which cause immediate coagulation necrosis, cryotherapy results in both immediate and delayed tissue injury and necrosis. 141. Furthermore, while RFA has controlled depth of penetration of heat energy, cryotherapy tissue injury can be modulated by altering cryogen dosimetry 142.

Two commercially available systems for endoscopic cryotherapy are available. The first system involves the release of liquid nitrogen through a heated endoscopic catheter resulting in gaseous expansion (CSA Medical, Baltimore, Maryland, USA)(Figure 2D). Compared to RFA, there are fewer and generally lower quality studies on liquid nitrogen cryoablation for BE neoplasia (Table 3). One year rates of CE-D are high (87-91%) but CE-IM rates (57-61%) are lower than those reported for RFA123, 128. Very limited data suggest durability of dysplasia eradication is reasonably high (94% at 3 years,85% at 5 years)127. Delayed recurrences occur in 18%, with a progression rate to ECA 4.0%, comparable to RFA127, 128. The serious adverse event rate is 0-3%, primarily due to rare perforation (1 case in early experience)143 and bleeding(1%) 123, 128. The incidence of post-ablation strictures requiring dilation is also low (0-9%).

The second cryotherapy system is a contact, balloon-based technique that uses nitrous oxide gas from capsules in a portable handheld device (Figure 2E)144. The gas inflates the balloon (enabling visualization through the balloon) and freezes targeted mucosa in contact with the balloon to -85 degrees Centigrade, creating discrete ice patches of approximately 1.5 to 2 cm^2 144. In a pilot feasibility trial, a single dose of cryogen delivered to the target BE mucosa resulted in full squamous regeneration in 100% of 10-second areas145. Another pilot feasibility trial reported 100% eradication of ESCN (LGIN, HGIN) after cryoballoon ablation using 8-12 seconds146. Clinical trials are ongoing in the United States, Europe, and China (www.clinicaltrials.gov).

Role of Surgical Therapy as an Adjunct to Endoscopic Therapy

For T1 esophageal cancer staged by EMR/ESD surgery should be reserved for cases with high risk of lymph-nodal metastasis 117. According to guidelines, sub-mucosal invasion in adenocarcinoma is an indication for definitive surgery, however good prognosis T1b EAC could be treated endoscopically especially in patients at high surgical risk 97, 147. For early ESCC, surgery may be elected in young and fit patients also for T1a m3 and T1b sm1. Esophagectomy can also be offered to operable patients with esophageal lesions that cannot be lifted during EMR, or dissected by ESD. Finally, it can be a rescue therapy for recurrences or metachronous neoplasia when all endoscopic therapies have been

unsuccessful. In the European and American cohort studies of ESD for BE-related neoplasia, esophagectomy was performed in 9.3 to 28% of patients107, 108.

Conclusions

Esophageal cancer fulfills many of the Junger criteria for screening now that endoscopic therapy is widely available and proven to be effective in curing early cancer and preventing progression of precursor lesions. However, esophageal cancer remains relatively uncommon, thus patient selection based on symptoms, family history and other predisposing risk factors is critical to improve cost-effectiveness. It is therefore imperative that the studies are performed in the relevant populations in order to avoid misleading estimates in sensitivity and specificity 148, 149. It is reasonable to evaluate new screening technologies in surveillance populations with a high prevalence of dysplasia and early cancer but this must then be followed by studies in the primary care setting alongside an evaluation of acceptability and health economics. These most promising advances have mainly focused on the detection of BE, however, given the global burden of ESCC accurate, low cost methods for primary screening for high-grade squamous dysplasia should be prioritized. Novel imaging techniques have provided impressive insight in to the mucosal structure to predict histology, however detection of inconspicuous dysplasia remains challenging. Given the continuous improvement in the knowledge of molecular events in esophageal carcinogenesis, molecular diagnosis holds great promises for the future either by directly imaging cancer-specific molecules, or combining advanced imaging with biomarkers or resolving differential interaction of diseased and normal tissue with incident light. Similarly, developing tools to resolve the tissue specific cancer risk is the most interesting avenue for future translational research in endoscopic imaging. Despite enormous progress made in the last decade in the field of endoscopic therapy, 10-20% of patients will fail endotherapy or recur after initial response and efforts need to focus on novel techniques to maximize response to endoscopic treatment. Finally, it is essential to develop tools, clinical and molecular, to stratify patients with borderline early cancer on staging endoscopic resection in order to avoid unnecessary surgery.

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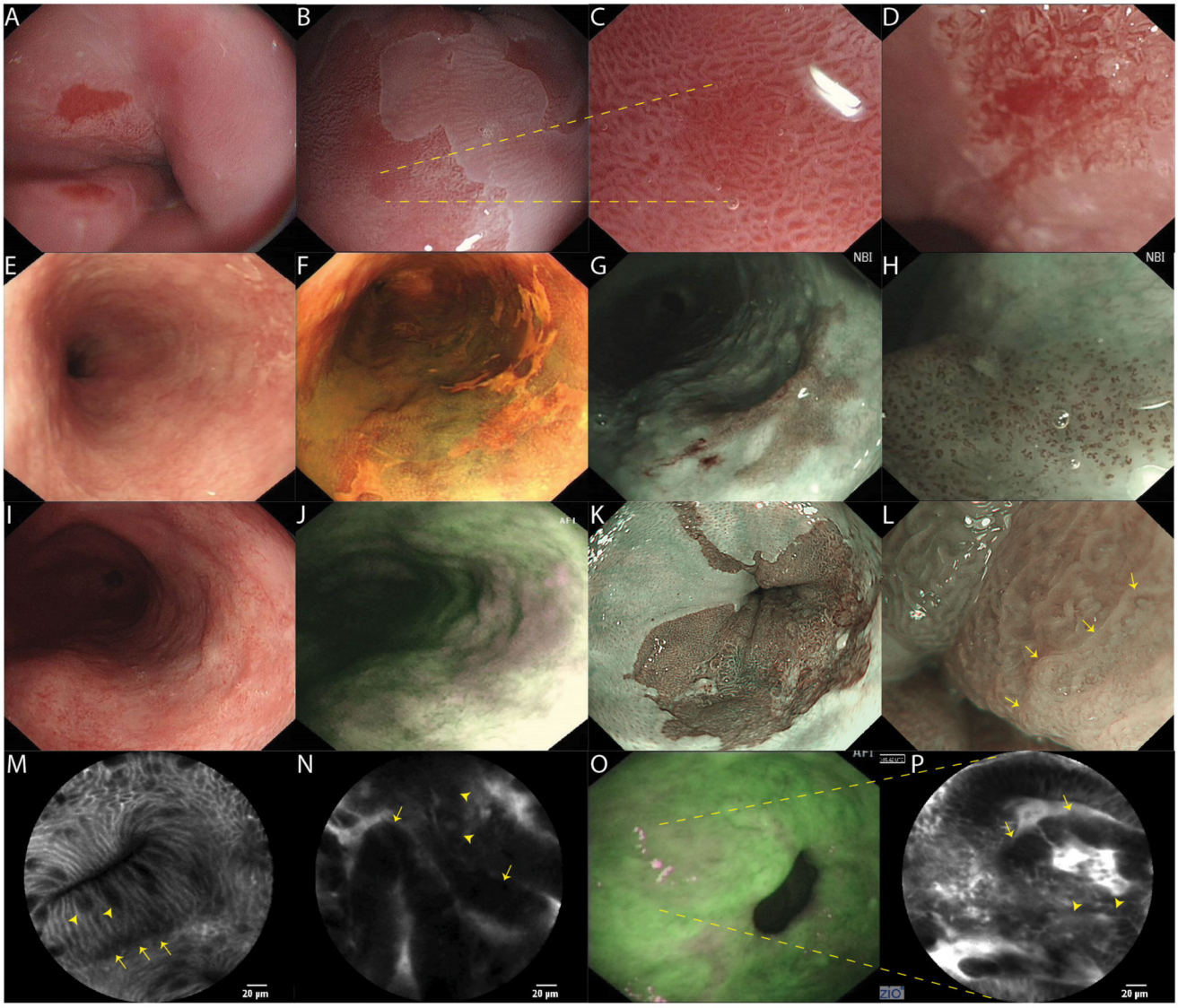

Figure 1. Advanced imaging techniques available in clinical practice to enhance detection of early esophageal neoplasia.

A-B. Examples of loss of acetowhitening after topic application of 2.5% acetic acid (AA). C-D. Magnification endoscopy in combination with AA allows identification of irregular mucosal pit for lesion delineation (area in C represents magnified view from B). E. Example of early flat esophageal squamous cell carcinoma (ESCC) difficult to delineate on WLE. F. Same case as E after topic application of 2.5% iodine (Lugol), which demonstrates voiding area and precisely delineates the lesion. G. Early ESCC appears on NBI as brownish discolouration of the mucosa. H. Same case as in G, where NBI magnification demonstrates Type V1 or B1 IPCLs in keeping with mucosal cancer. I. Example of flat early esophageal adenocarcinoma (EA) difficult to delineate on WLE. J. Same case as in I, where AFI demonstrate a clear positive area at the 3o'clock position extending for 25% of the circumference. K. Example of early EA well delineated by non-magnified NBI. L. Same case as in K; magnification NBI allows interrogation of mucosal pit and superficial

vasculature to define the demarcation line (arrows). M. pCLE view of non-dysplastic Barrett's esophagus (BE) with regular cells, regular glandular margins (arrows) and clearly visible goblet cells (arrowheads). N. Example of HGD on pCLE analysis with irregular glands (arrows), pleomorphic cells (arrowheads) and loss of goblet cells. O-P. Example of AFI directed pCLE on inconspicuous BE. pCLE shows irregular cells (arrowheads) and glands (arrows), suspicious for dysplasia. Histology confirmed low-grade dysplasia.

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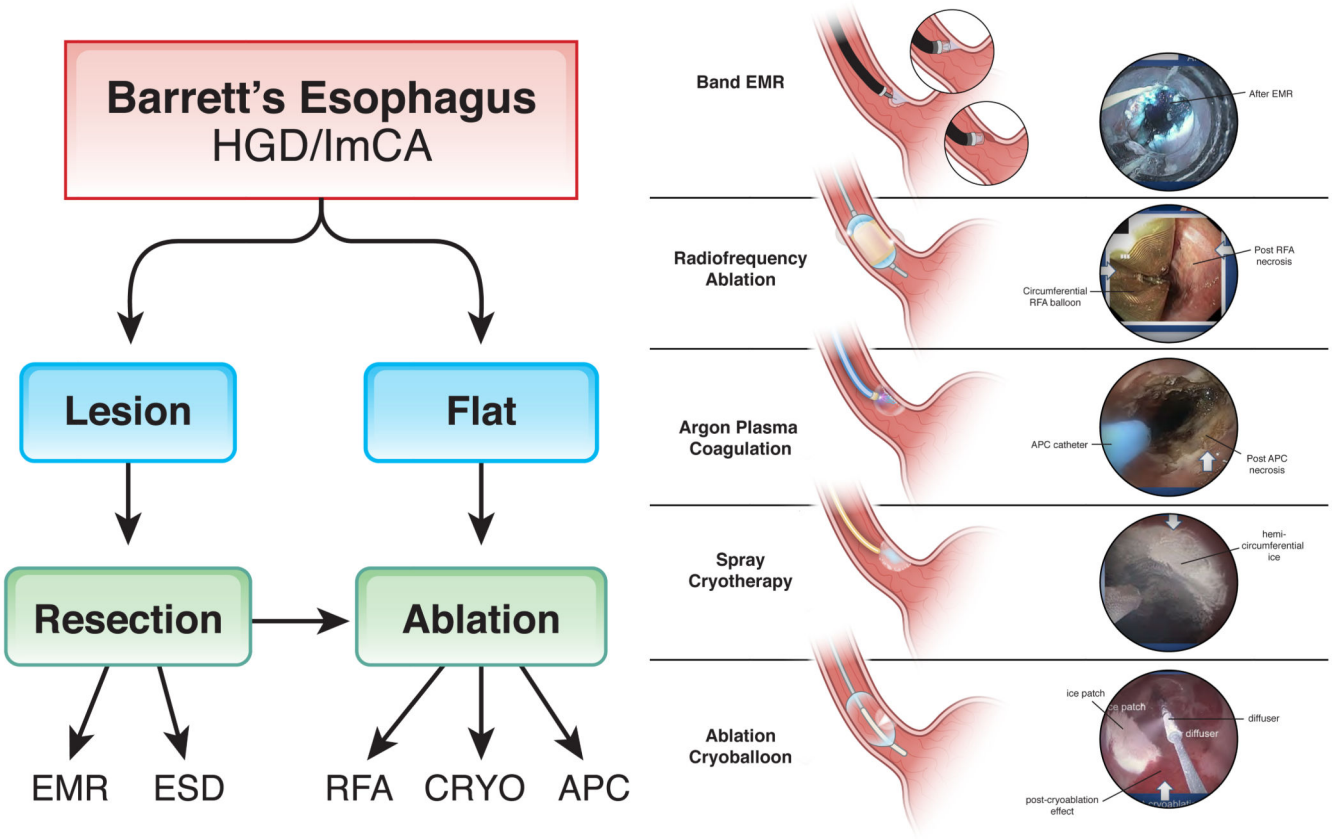

Figure 2. Endoscopic techniques for eradication of oesophageal early neoplasia.

A Band endoscopic mucosal resection (EMR) involves suction and ligation (banding) of a target lesion, with or without prior submucosal injection, followed resection using snare polypectomy technique. Endoscopic photo shows the endoscopic view of the submucosa through the banding device after complete resection of well-differentiated adenocarcinoma. B. Argon plasma coagulation (APC) involves conduction of heat energy with argon gas to the mucosa (arrow). Endoscopic image shows the APC catheter and white coagulation necrosis of treated BE mucosa (arrow). C. RFA involves the application of a preset amount of heat energy (12 Joules) through electrodes on a circumferential (Halo 360) ablation catheter (arrow) inflated to make contact with the esophageal mucosa. Endoscopic image of post-RFA necrosis. D. Liquid nitrogen spray cryotherapy involves release of liquid nitrogen that expands to gas and freezes large areas of tissue to -196 degrees Celsius. The dosing of liquid nitrogen cryogen has varied from 15-20 seconds of ice, followed by a timed minimum 45 seconds of thaw and repeated for 3 cycles150. Endoscopic image of a hemi-circumferential patch of ice on the esophageal mucosa. E. The cryoballoon ablation system includes a portable hand-held reusable controller that delivers nitrous oxide gas into a low pressure compliant 30 mm long oval shaped balloon at the end of a disposable balloon catheter passed through the endoscope channel. The balloon at the end of the catheter is inflated and simultaneously cooled by the gas expansion. The cryogen is directed towards a specific location by rotation of the diffuser. Endoscopic image shows the endoscopic view

through the cryoballoon with a focal ice patch and thawed treated mucosa with post cryotherapy red color change (arrow).

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Table 1

Summary of characteristics of different screening tests for esophageal cancer

	Accuracy	Cost-effectiveness	Suitable for primary care	Scientific evidence
Conventional Endoscopy (EGD)	Gold standard - •Good image quality •Histologic diagnosis with sampling bias	Very Low - •High direct and indirect costs	No - •Not portable, •Sedation required	Yes - •High diagnostic yield in selected groups
Trans-nasal endoscopy (TNE)	Good - •Acceptable image quality •Small or no biopsy sampling	Unknown - •Low direct and indirect costs	Yes - •For office-based system •Expertise required to perform test	Yes - •Generally preferred over endoscopy •Feasible in community-based studies
Capsule endoscopy (CE)	Good - •High frame rate for new generation •No tissue sampling	Low - •Comparative studies show EGD is preferred to CE	Yes - •Expertise required for image analysis	Limited - •Lack of community-based studies
Cytosponge	Good - •Tissue based diagnosis with pan-esophageal sampling •Molecular diagnosis possible	Yes - •ICER for cytosponge followed by EGD ≈$30,000	Yes - •Nurse led clinic •Central laboratory	Yes - •Feasible and well tolerated in community-based studies •Large studies in secondary care
Circulating or stool markers	Unknown	Unknown - •Low direct and indirect costs	Yes - •Nurse led clinic •Central laboratory	Limited - •Small pilot studies only
Volatile compounds in breath	Unknown	Unknown - •Low indirect costs •Limited data on direct costs	Yes - •Nurse led clinic •Central laboratory	Limited - •Small pilot studies only

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Table 2

Summary of the evidence for advanced imaging modalities in the detection of esophageal HGD or cancer. Only techniques investigated in large studies were included.

Technique	Type	Disease	Endoscopy Features	Sesitivity /Specificity*	Evidence Quality (Grade)
Acetic acid (2.5%)	Conventional Chromo	Early EA	Loss of aceto-whitening Irregular mucosal pit	Sens: 92 – 96.6% Spec: 84 – 94.6%	Low
Lugol (2-3%)	Conventional Chromo	Early ESCC	Lugol voiding lesion >5mm Pink sign	Sens: 80 – 100% Spec: 64 – 94%	Moderate
NBI	Electronic Chromo	Early EA	Irregular mucosal pit and microvasculature	Sens: 91 - 94.2% Spec: 85 - 94.4%	High
		Early ESCC	Brownish area Irregular IPCLs	Sens: 82 – 88% Spec: 75 – 95%	Moderate
AFI	Electronic Chromo	Early EA	Red/magenta within green background	Sens: 79 - 83% Spec: 46%	High
		Early ESCC	Red/magenta within green background	Sens: N/A Spec: N/A	Low
CLE	Endoscopic microscopy	Early EA	Cellular and architectural changes	Sens: 90% - 95% Spec: 67 - 92%	High
		Early ESCC	Surface maturation score IPCL and cell morphology	Sens: 94 – 95.7% Spec: 90%	Low

*Based on well-designed studies and meta-analyses if available. Abbreviations: Chromo (chromoendoscopy), EA (esophageal adenocarcinoma), ESCC (esophageal squamous cell carcinoma), Sens (sensitivity), Spec (specificity) IPCL (intra-papillary capillary loops)

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Table 3

Comparison of Efficacy of Ablative Techniques for Eradication of BE and Related Neoplasia

Study	Study Design	N	Prior EMR	Patient Population	Number of Treatments (Median)	Average Maximum BE Length (cm)	CE-HGD	CE-LGD	CE-D	CE-IM
APC (Manner 2014)	RCT[1]	33	100%	33 ND (prior HGD/IMC)	4.0	5.9	NR	NR	NR	79%
H-APC (Manner 2014)	NRCT[1]	50	100%	50 ND	3.5	4.9	NR	NR	NR	82% 78%
RFA (Shaheen 2009)	RCT[2]	84	NR	42 HGD, 42 LGD	3.5	4.6 HGD 5.3 LGD	81% 90%	90% 95%	86% 92%	77% 83%
RFA (Shaheen 2011)	Prospective cohort[3]	119	8.4%	54 HGD, 52 LGD	3.5	5.3 HGD 4.6 LGD	95% 96%	98% yr2 100% yr3*	95% 98%	93% 92%
RFA (van Vilsteren 2011)	RCT[4]	22	81%	15 IMC 7 HGD	3.0	3.0	NR	NA	96%[4]	96%[4]
RFA (Haidry 2013)	Prospective cohort	355	49%	26 IMC 241 HGD, 12 LGD	2.5	5.8	86%	83%	81%[5]	62%[4]
RFA (Phoa 2014)	RCT[2]	70	0	70 LGD	3.0	4	NA	93%	93%[5]	88%[4]
LNC (Shaheen 2010)	Retrospective cohort	98	25%	60 HGD	4.0	5	97%	97%	87%	57%
LNC (Ghorbani 2015)	Retrospective cohort	96	20%	57 HGD, 23 LGD	3.5 HGD 2.9 LGD	4.1 HGD 5.1 LGD	91%	81%	91%	61%
LNC (Ramay 2017)	Retrospective cohort	50	28%	50 (46 HGD, 4 T1a ECA)	3.0	3.5	96% 93%	NR	94% 88%	82% 75%
CC (Canto 2015)	Retrospective cohort	64	28%	3 IMC 18 HGD	4	5.9	100%	NA	95%	70%

NRT = non-randomized uncontrolled clinical trial; RCT = randomized controlled clinical trial;
NA = not applicable, NR = not reported
IMC = intramucosal adenocarcinoma; HGD = high grade dysplasia
CE-D = complete eradication of dysplasia; CE-IM = complete eradication of intestinal metaplasia
APC = argon plasma coagulation, H-APC = hybrid APC, LNC = liquid nitrogen cryotherapy, CC= carbon dioxide cryotherapy

[1]Patients with residual non-dysplastic (ND) BE with prior neoplasia eradicated by EMR

[2]Included only patients with non-nodular BE

[3]Cohort extension of Ablation of Intestinal Metaplasia (AIM) trial patients who achieved CE-IM at 1 year (Shaheen 2009)

[4]"Rescue" therapies performed after initiation of RFA