New Endoscopic Diagnosis and Treatment Options for Early Esophageal Cancer

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Abstract

Recent advances in endoscopic technology have increased detection rates of early esophageal cancer. Novel imaging techniques, such as narrow band imaging, autofluorescence imaging, confocal laser endomicroscopy and optical coherence tomography, have been recently introduced that may be taking us closer to the “optical biopsy” for diagnosis of esophageal lesions. Along with the increased endoscopic detection rates, more and more early esophageal lesions have been also treated by endoscopic options. There are now long-term randomized controlled data concerning the effectiveness of ablative approaches (photodynamic therapy, cryotherapy and radiofrequency ablation); however, the ablation does not provide a tissue specimen for histopathological assessment. Unlike ablative techniques, endoscopic resection permits histopathological assessment, similar to surgery. As a new resection technique, endoscopic submucosal dissection results in complete eradication of all diseases and may translate to a lower recurrence rate than conventional endoscopic mucosal resection procedure.

Keywords: Early esophageal cancer; Optical biopsy; Endoscopic therapy; Endoscopic submucosal dissection

Abbreviations: HGIN: High-Grade Intraepithelial Neoplasia; HRE: High-Resolution Endoscopy; NBI: Narrow Band Imaging; EAC: Esophageal Adenocarcinoma; BE: Barrett’s Esophagus; SCC: Squamous Cell Cancer; AFI: Autofluorescence Imaging; CLE: Confocal Laser Endomicroscopy; OCT: Optical Coherence Tomography; EUS: Endoscopic Ultrasound; PDT: Photodynamic Therapy; RFA: Radiofrequency Ablation; ER: Endoscopic Resection; EMR: Endoscopic Mucosal Resection; ESD: Endoscopic Submucosal Dissection

Introduction

Early esophageal cancer is defined as tumor limited to the mucosa or submucosa, and without lymphatic spread or distant metastasis. Intraepithelial neoplasia, including low-grade and high-grade intraepithelial neoplasia (HGIN), is defined as the precancerous change of esophageal cancer. Recent advances in endoscopic technology have increased detection rates of early esophageal cancer. In 31% of patients the esophageal cancer is detected early in situ. Along with endoscopic detection, more and more early esophageal lesions have been also treated by endoscopic options. Compared with conventional esophagectomy, endoscopic therapies for intraepithelial neoplasia and early esophageal cancer are viable alternatives with significantly lower morbidities. Endoscopic diagnosis and treatment for early esophageal cancer has represented the trend of future. Thus, this review summarizes recent progress on endoscopic diagnosis and treatment options for early esophageal cancer.

Advances in Endoscopic Diagnosis

The quality of the endoscopic image is an important factor in the detection of small esophageal lesions, which may harbor neoplasia or early esophageal cancer. Novel imaging techniques have been recently introduced that may be taking us closer to the “optical biopsy.” The capabilities of the “perfect” imaging modality would include the following characteristics: (1) detect dysplastic changes; (2) have microscopic resolution; (3) be able to obtain real-time images; (4) differentiate dysplasia from inflammation-related changes; (5) localize dysplasia for targeted biopsies; (6) be inexpensive [1]. Unfortunately, no one imaging modality exhibits all of these characteristics.

High-Resolution and Magnified Endoscopy

The endoscopic detection of abnormal mucosa is paramount. Conventional white light endoscopic images less reliably detect mucosal histology. Both high-resolution endoscopy (HRE) and magnification endoscopy are available and have significantly increased the sensitivity and specificity in the differentiation of mucosal lesions [2]. High-resolution endoscopes are now capable of discriminating objects that are as small as 0.01 mm. Magnified endoscopy can produce an increase in image size of up to 105-fold. These advances allow the possibility of detecting changes in the mucosa or potentially characterizing dysplasia and facilitating directed biopsies [3].

Narrow Band Imaging (NBI)

NBI uses an optical filter to select blue (440-460 nm) and green (540-560 nm) wavelength light. This technology improves the visibility of superficial capillaries and mucosal structures by optimizing the absorbance and scattering characteristics of light [4]. NBI allows clear visualization of the mucosa pit patterns and capillary patterns, and facilitates targeted biopsies. The authors of a recent meta-analysis reported the pooled sensitivity and specificity for the discrimination of HGIN or esophageal adenocarcinoma (EAC) in a field of Barrett’s esophagus (BE) as 96% and 94%, respectively. Compared with staining chromoendoscopy (methylene blue, indigo carmine, etc), which has been questioned to be no better than random biopsies [5], NBI offers advantages in detecting subtle mucosal lesions due to HGIN / EAC and in enabling directed biopsies to areas of concern. This modality has been proven to aid in the diagnostic precision for HGIN or EAC compared with white light endoscopy alone [6]. Recently, the authors from Asia-Pacific countries also demonstrated that NBI is useful for detection and characterization of superficial esophageal squamous cell cancer (SCC), and could replace chromoendoscopy in routine examination because it is easy to use and adds much information to conventional white light.

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of Barrett's esophagus mucosa [20]. In a recent prospective randomized
regarded as non-inferior to endoscopic biopsy in excluding neoplasia
biopsy for evaluation of neoplasia in BE, probe-based CLE could be
in BE or EAC [17-19]. Compared with standard four-quadrant
types of epithelial cells and differentiate both dysplasia and neoplasia
layer in question [16]. CLE has the potential to distinguish different
"optical biopsy" for histologic examination of the superficial mucosal
channel, and a low-power laser is trained on to the mucosa. It is the
contrast agent, a probe is introduced through the endoscopic working
modality that is able to generate high-resolution microscopic-like images
histological analysis. CLE is a recently released endoscopic imaging
target suspicious areas to obtain biopsy and resection specimens for
esophageal cancer were shown in Figure 2.

Autofluorescence Imaging (AFI)

AFI is a technology that exploits certain endogenous substances
in the tissue (fluorophores) which, when excited by light, emit light of
a longer wavelength than the exciting light [8]. AFI produces images
in which normal esophageal squamous and nondysplastic Barrett's
esophagus appear green, areas of HGIN/ EAC appear bluish- purple,
and squamous islands amidst intestinal metaplasia appear pinkish.
Advantages to AFI include its potential as a `red flag' technique and
the fact that it requires no additional contrast agent [9,10]. The main
limitation is the high false positive rate [9,11]. Thus, other endoscopic
options are needed to increase the accuracy of detecting suspicious
lesions. Autofluorescence intensity and abnormal white light appearance
of areas identified by AFI correlated with true positives [12]. A proof-of-
principle study confirmed the feasibility of combining AFI and NBI for
improving the accuracy of the endoscopic detection of HGIN in BE [9].
A trimodal prototype system with AFI and NBI integrated into a HRE
doscope was more effective than standard endoscopy in indentifying
early-stage neoplasia in BE. AFI detected more lesions not seen with
HRE, and NBI decreased the false-positive rate [13,14]. However, the
use of AFI as part of a trimodal system (HRE, AFI, and NBI) that can
detect occult neoplasia and assist in endoscopic mucosal resection
warrants further investigation [15]. Representative AFI images of early
esophageal cancer were shown in Figure 2.

Confocal Laser Endomicroscopy (CLE)

NBI, AFI, and chromoendoscopy allow the endoscopist to
target suspicious areas to obtain biopsy and resection specimens for
histological analysis. CLE is a recently released endoscopic imaging
modality that is able to generate high-resolution microscopic-like images
of the mucosal layer. After the patient is injected with an intravenous
contrast agent, a probe is introduced through the endoscopic working
channel, and a low-power laser is trained on to the mucosa. It is the
detection of the fluorescent light back from the tissue that provides an
“optical biopsy” for histologic examination of the superficial mucosal
layer in question [16]. CLE has the potential to distinguish different
types of epithelial cells and differentiate both dysplasia and neoplasia
in BE or EAC [17-19]. Compared with standard four-quadrant
biopsy for evaluation of neoplasia in BE, probe-based CLE could be
regarded as non-inferior to endoscopic biopsy in excluding neoplasia
of Barrett's esophagus mucosa [20]. In a recent prospective randomized
controlled trial, CLE with targeted biopsy significantly improved the
diagnostic yield for endoscopically apparent BE neoplasia compared to
a standard endoscopy with a random-biopsy protocol. CLE with
targeted biopsy also greatly reduced the number of biopsies needed
per patient and allows some patients without neoplasia to completely
forgo mucosal biopsy [21]. In a pilot study of patients with superficial
esophageal SCC, CLE could also be used to distinguish cancers from
normal epithelium, which gives it potential value for early detection of
esophageal carcinoma. The difficulty in obtaining good images in the
esophagus by CLE was a latent problem [22].

It is important to remember that this approach is examiner
dependent because the interpretation of the “optical biopsy” is
performed in real time in vivo. Endoscopists who perform CLE must
have some familiarity with tissue architecture of the gastrointestinal
tract in order to interpret images [23]. Due to its low positive predictive
values and sensitivity, CLE may currently not replace standard biopsy
techniques for the diagnosis of esophageal lesions. Further technical
development of CLE and a better understanding of its role in relation to
other imaging technologies are necessary [20].

Optical Coherence Tomography (OCT)

OCT uses near-infrared light to produce high-resolution (10 µm
axial resolution) cross-sectional images of gastrointestinal mucosa with
depth of 1-2 mm. OCT is also performed by placing a probe through
the working channel of an endoscope and is a noninvasive technique
able to capture micrometer resolution of biological tissues with
3-dimensional image output. OCT processes coherent back scattered
light providing real-time in-vivo microscopic resolution of subsurface
tissue architectural morphology [24]. It has been investigated for
detecting dysplasia in BE with a 78% accuracy in a prospective,
double-blinded study [25]. A preliminary descriptive clinical study
demonstrated the feasibility of carrying out ultrahigh resolution
OCT imaging in conjunction with standard endoscopy for in vivo
real-time imaging of Barrett's esophagus, dysplasia, and esophageal
adenocarcinoma [26]. In addition, ultrahigh resolution OCT imaging
is capable of identifying subquamous Barrett's epithelium in patients
who have undergone ablative therapy, which is not visible on standard
endoscopic examination [27]. In superficial esophageal SCC, OCT
might also be useful for the preoperative staging with a high degree of
accuracy [28].

Problems identified were the variability in endoscopists’ accuracy
rates, difficulty in real-time interpretation, and the need for refined

Figure 1: Representative NBI images of early esophageal cancer. A. Endoscopic examination with narrow-band imaging reveals the presence of brownish epithelium. B. Endoscopic examination with narrow-band imaging reveals the brownish dots. C. The presence of tortuous intraepithelial papillary capillary loop (IPCL), caliber change in IPCL and variety in IPCL shapes.
It has also been investigated the accuracy in correlation with histology in BE in a study [43]. With 450-fold magnification, only 23% of images were sufficiently interpretable to identify characteristics of neoplasia, whereas for 1125-fold magnification, it was 41%.

However, when not supported by macroscopic evidence, endoscopic histology using endocytoscopy lacked sufficient image quality to be of use in identifying neoplastic areas [43]. Moreover, it is also not surprising that the quality of the majority of images was poor, because of the difficulty of maintaining a moving organ in focus using an endoscope. In addition, endoscopists are not trained in assessment of cytology, and a pathologist was needed. Appropriate preconditioning to constantly obtain sufficient image quality and universal criteria for endoscopic diagnosis of various diseases are essential before clinical application [42].

Endoscopic Ultrasound (EUS)

The precise differentiation of esophageal wall layers, direct imaging of the surrounding organs and tissues, and tissue sampling with fine needle aspiration has allowed EUS to play a pivotal role in the staging of patients with esophageal cancer. EUS accuracy in esophageal cancer staging has been evaluated in multiple studies; it was found to be the most accurate imaging modality in the assessment of tumor invasion and locoregional lymph node status [44].

The recent increase in the incidence of superficial esophageal cancer and promising developments in potentially curative endoscopic therapies have placed EUS in a central position with regard to decision making. EUS has emerged as a requisite in the staging of patients with early esophageal cancer. In a meta-analysis, the pooled sensitivity and specificity to diagnose T1 stage cancer was 81.6% and 99.4%, respectively, which is much lower than for more advanced T stages [45]. The largest study prospectively evaluating staging in early esophageal cancer using high-frequency ultrasound probes revealed an overall accuracy of 80%. However, the sensitivity for submucosal invasion fell to 48% [46]. The location of tumor with submucosal invasion and the depth of submucosal invasion were found to play an important role in staging.

However with current technology, EUS – even with high-frequency probes has limited accuracy in differentiating early tumors that are confined to the mucosa from those that invade the submucosa, and it is used principally to screen for lymphatic metastases in the setting of early-stage disease [44]. In addition, the accuracy of EUS is operator-dependent. Operator's experience and machine-dependent factors may play an important role in the accurate staging of esophageal carcinoma [47]. Improvement in technology will probably decrease instrument-dependent factors causing artifacts.

Advances in Endoscopic Therapy

Endoscopic therapy has become a viable alternative for patients with neoplasia or early esophageal cacer due to the low rates of lymphatic or hematogenous dissemination, corroborated with the adverse effects of esophagectomy [48]. These treatments used either alone or in combination with other techniques, can be grouped into two categories: (1) ablative and (2) non-ablative. Ablative approaches, which use different energy sources to obliterate the lesions, include photodynamic therapy, radiofrequency ablation, argon plasma coagulation, and cryotherapy. Non-ablative endoscopic approaches primarily comprise endoscopic resection and variations of this technique.
Photodynamic Therapy (PDT)

PDT has been the most investigated of all the ablative techniques developed for dysplasia and early esophageal cancer treatment. A photosensitizing agent selectively absorbed by fast-growing cells, such as cancer cells, is introduced intravenously or orally. Activation of the photosensitizer is achieved by endoscopically applied laser directly to the malignant tumor. This results in the formation of free oxygen radicals in the tumor tissue leading to ischemic necrosis of the tumor cells. A prospective randomized study showed a significant difference for the study group treated with PDT and omeprazole comparative with the group treated with omeprazole only regarding the ablation of high grade dysplasia and the recurrence of neoplasia [49]. After PDT with Photofrin and red light, the adverse effects were minimal and the median survival was 60.5 months. A system review also showed PDT is effective for the ablation of dysplasia in Barrett’s esophagus, although the frequency of adverse events is quite high [50]. The efficacy of PDT for superficial esophageal SCC has been evaluated in multiple studies [51-53]. PDT eradicated early esophageal SCC (T1a and T1a) of the esophagus efficiently [51,52]. A long-term follow-up study revealed that PDT was a potentially curative treatment for large superficial esophageal SCC. Complete remission was achieved in 87% patients, and after a median follow-up period of 64 months after PDT, the overall 5-year survival rate was 76% [53].

However, it has been limited by serious side effects including prolonged cutaneous photosensitivity, stricture formation and recurrence. A long-term follow-up study demonstrated that only up to one-third of patients could be successfully treated with PDT without having a recurrence [54]. In addition, almost one-half developed very symptomatic and refractory esophageal strictures. Recurrence of dysplasia/neoplasia after PDT ablation was associated with advanced age, smoking, and residual BE [55]. The incidence of severe stricture was related to the light dose. Decreasing the light dose below 115 J/cm appeared to result in a reduced incidence rate of severe stricture but higher relative frequencies of residual HGIN/T1 in BE [56]. Moreover, perhaps the biggest drawback of PDT ablation therapies for BE is the well-recognized risk that the regenerating squamous epithelium could cover residual underlying Barrett’s esophagus mucosa, giving rise to the problem of ‘buried glands’. Buried glands have been reported in up to 24% of patients following 5-aminolaevulinic acid PDT [57]. There is concern that such glands are difficult to access at endoscopic surveillance, but might still be at risk of malignant progression. The recent development of radiofrequency ablation (RFA) might have gone some way towards addressing the problem of ‘buried glands’.

Radiofrequency Ablation (RFA)

RFA delivers the direct application of thermal energy to the mucosa of the esophagus. This is accomplished with either an ablation catheter for circumferential treatment or an endoscope mounted device for more focal ablation. The energy delivered provides uniform treatment to a depth of approximately 500 μm. Therefore, the depth of treatment does not enter into the submucosal layer, and the risk of stenosis is reduced.

The authors of initial pilot studies reported complete eradication of HGIN in up to 90% of patients [58]. These encouraging results led to a multicenter, sham-controlled trial in patients with dysplastic BE [59-61]. In this trial, 127 highly selected patients with low-grade and HGIN were randomized to treatment with RFA or a sham endoscopic ablation. Primary outcomes at 12 months showed that in those patients with HGIN, 81% had complete eradication of dysplasia with ablation compared with 19% in the control arm (P<0.001). In addition, sham-controlled trial of RFA was associated with improvement in disease-specific health-related quality of life [60]. During a mean time of 3.05 years follow-up, dysplasia remained eradicated in >85% of patients and intestinal metaplasia in >75%, without maintenance RFA. Serious adverse events occurred in 4 of 119 subjects (3.4%); the rate of stricture was 7.6%. There was no cancer-related morbidity or mortality [61]. So in subjects with dysplastic BE, RFA therapy has an acceptable safety profile, is durable, and is associated with a low rate of disease progression, for up to 3 years. Besides, some studies also suggested that RFA for squamous HGIN and early esophageal SCC was feasible and effective, speculating that RFA might also be suited for early squamous neoplasia of the esophagus [62,63].

An inherent weakness of RFA ablation, as with all other nonresectional endoscopic ablation techniques, is that it does not provide a tissue specimen for histopathological assessment. This means that if RFA is used for the treatment of intramucosal cancer, there is no way to assess the depth of tumor invasion or to confirm that the tumor treated is actually confined to the mucosa.

Cryotherapy

Liquid nitrogen or freezing carbon dioxide gas is sprayed directly onto the tumour via an open-tipped catheter. The targeted tissue is “frozen”, and then allowed to thaw. Repeating the ‘freeze and thaw’ cycle subsequently destroys the lesion. The authors of a pilot study demonstrated complete reversal of BE with dysplasia in 82% of patients treated with cryotherapy [64]. In a recent prospective open-label study, 31 patients with either HGIN (n = 26) or intramucosal carcinoma (n = 5) who were nonoperative candidates were treated with cryotherapy [65]. At a median follow-up of 12 months, 90% of patients demonstrated at least a partial response. A complete response rate was seen in 68% of those with HGIN and 80% of those with carcinoma. The authors of another slightly larger retrospective cohort study demonstrated that those patients completing all planned treatments had 97% eradication of HGIN [66]. The most common complaint was chest pain, followed by dysphagia, odynophagia, and sore throat [67]. Although endoscopic spray cryotherapy may be a promising ablative modality for treatment of BE and early esophageal cancer, limitations of current studies include small sample sizes and short durations of follow up, and further studies are needed to validate the promising early results.

Endoscopic Resection (ER)

Endoscopic resection (ER) is the general term for all of the different resection techniques used to treat neoplastic and uncertain lesions in the gastrointestinal tract. Endoscopic resection results in complete eradication of all disease with a possible restoration of the molecular baseline within the neosquamous epithelium. This may translate to a lower recurrence rate. In contrast to ablative treatment methods such as PDT and RFA, ER allows histological assessment of the resected specimen in order to assess the depth of infiltration of the tumour and freedom from neoplasia at the lateral and (more importantly) basal margins, imitating the surgical situation. These significant advantages of ER are the main reason why ER should be preferred to ablative treatment methods, even RFA, whenever possible, especially bearing in mind the low accuracy of EUS regarding local tumour staging [68].

The conventional ER procedure is endoscopic mucosal resection (EMR). Several EMR techniques of endoscopic resection have been described, including with or without a suction device [68]. The different techniques have shown very similar results in terms of the specimen resected, and the success of the procedure. Most studies report complete...
resection rates of about 80–90%, but with strict patient selection, R0 resection can be achieved in 98–100% of patients [69].

The major drawback of EMR technique appears to be that only small lesions with a diameter of less than 20 mm can be resected en bloc with tumour-free lateral margins. Ulcerated lesions often have fibrosis attaching the submucosa to the lamina muscularis propria, resulting in failure of the lesion to lift. In these cases, EMR is not advisable, or should only be performed with caution. Larger lesions can usually be resected completely using the piecemeal technique, but this method appears to be associated with a higher recurrence rate because of small neoplastic residues resulting from insufficient overlapping of the resection areas. At a median follow-up of 61 months, Pech et al. [70] found metachronous tumors in 21% of 231 patients, while the Mayo Clinic reported recurrences in 12% of 132 patients over a similar time-frame [71]. Similarly a follow-up study in Japan found metachronous lesions in up to 15% of patients undergoing EMR for squamous cell cancer [72]. In addition, en bloc resection allows more accurate histological evaluation of the neoplastic lesion, especially of the lateral and basal margins. A new resection technique, endoscopic submucosal dissection (ESD), was therefore developed.

The ESD procedure is a method using an electronic knife to dissect the submucosal layer underneath the carcinoma in order to obtain a large resection specimen with the neoplasm resected en bloc. It is a three-step process in which the tumour is first marked using electrocautery, then raised by injecting a saline solution below it, and finally excised using an electrocautery knife [73]. The endoscopic submucosal dissection (ESD) procedure for an early cancer of median esophagus was shown in Figure 3.

Recently, a retrospective study from Japan assessed the long-term outcomes of ESD for esophageal squamous cell neoplasms, and revealed that ESD is a potentially curative treatment for superficial esophageal squamous cell neoplasms [74]. In this study, 107 superficial esophageal squamous cell neoplasms in 84 patients were treated by ESD. The rates of en bloc resection and complete resection were 100% and 88%, respectively. One patient had local recurrence 6 months after ESD. In 2 patients with intramucosal invasive carcinomas in the muscularis mucosa, distant metastases were observed 9 and 18 months after ESD. During the median observation of 632 days, 3 patients died of esophageal carcinoma. Another study from Western also confirmed that ESD is a potentially curative treatment for superficial esophageal squamous cell neoplasia [75]. Besides, studies also showed that ESD can be adequately adopted as an effective treatment for superficial adenocarcinomas at the esophagogastric junction, with no local or distant recurrences observed in any patient achieving curative resection during long-term follow-up [76,77].

Some studies comparing ESD and conventional EMR in early esophageal cancer have been published. A retrospective cohort study from Japan involved 300 patients with esophageal SCC who underwent either EMR (n = 184) or ESD (n = 116). En bloc resection and the local recurrence rate were significantly better in the ESD group (P = 0.0009 and 0.065, respectively). During the median observation of 65 months, ESD gave fewer local recurrence compared with EMR [78]. Another report also demonstrated that larger superficial esophageal tumors (>15 mm) should be treated with ESD to reduce local recurrence [79]. Some reports demonstrate that ESD may be associated with a higher risk of strictures and an esophageal perforation rate compared with EMR [80], however, in comparative medical center, these complication rates did not differ significantly [77-79]. Most complications can be readily dealt with by endoscopic dilatation or clips. Only few complications need to be dealt with by surgery.

Summary

The rapid development of endoscopic technology has improved current endoscopic diagnostic and therapeutic capabilities for early esophageal cancer. Compared with chromoendoscopy, using High-resolution and magnified endoscopy, NBI, AFI or CLE appears to be ease of use and the possibility of targeted biopsies as subtle mucosal lesions are detected. OCT, Spectroscopy and Endocytoscopy remain experimental. EUS has emerged as a requisite in the staging of patients with esophageal lesions. In terms of endoscopic treatment, there are now long-term randomized controlled data concerning the effectiveness of PDT and cryotherapy; however, the ablation may not be complete, and complications such as strictures and recurrence remain problematic. Endoscopic radiofrequency ablation appears a durable
safety profile, which is associated with a low rate of disease progression compared with other ablative techniques. Unlike ablative techniques, endoscopic resection permits histopathological assessment, similar to surgery. These significant advantages of ER are the main reason why ER should be preferred to ablative treatment methods. As a new resection technique, ESD results in complete eradication of all disease and may translate to a lower recurrence rate than conventional EMR procedure.

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