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Detection and staging of esophageal cancers

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Abstract

Purpose of review—Technology for detection and staging of esophageal cancer has made significant strides advances in the past 2 years. These advances have led to the enhanced selection of appropriate treatments for esophageal cancer. Cancers that are discovered at an early stage can be treated with endoscopic therapy, whereas advanced cancers are primarily treated with chemotherapy and radiation.

Recent findings—Detection of esophageal cancer can be enhanced by two major mechanisms: one is by enhancing the lesion, which has typically been done using vital dyes and the other is by changing the method of imaging of the lesion, which has been accomplished by the use of several technologies including fluorescence and optical coherence tomography. Neither of these techniques has been proven, but some investigators have been able to use them to enhance cancer detection. Similar technologies have been applied to staging esophageal cancer. The optical imaging devices also have the potential to stage mucosa-based malignancy. The use of positron emission tomography has been the most recent development that may have application for advanced cancer. Endoscopic ultrasonography has also been improved in resolution and ability to perform fine needle aspiration. The most significant development for staging early cancers is mucosal resection. Finally, by using mucosal resection techniques, the depth of tumor invasion can be established by histology, which allows gastroenterologists to treat early cancers with greater confidence regarding rates of metastatic disease.

Summary—Early detection of esophageal cancer can be enhanced by the use of vital dyes for mucosal staining, but the advancement of novel optical diagnostic strategies may be more suitable for clinical use. The primary advantage of these new staging methods is to clearly identify early stage cancer that potentially can be treated without traditional surgical resection techniques. More advanced cancers can be staged with positron emission tomography, but definitive studies demonstrating its role are still lacking.

Keywords

esophageal cancer; staging; adenocarcinoma

Introduction

The advent of new endoscopic therapies for early esophageal cancer has led to increasing demands on staging and detection of esophageal cancer. Esophageal cancer has been increasing in incidence in the past decade. Although mortality rates are still high, screening and surveillance for preneoplastic conditions has led to the detection of early cancers and new

staging methods for advanced cancers. In this review, the most recent developments in staging and detection of esophageal cancer are discussed.

Detection and staging of esophageal cancer are interlinked because earlier detection of cancer leads to an early stage of disease found at diagnosis [1]. The goal of early detection depends on identifying those patients at risk of disease. These issues have become even more important because patients with early cancers can now be treated without the need for esophagectomy using endoscopic techniques such as endoscopic mucosectomy and photodynamic therapy [2]. To implement novel therapies, the detection and staging of esophageal cancer have become critical. Even the therapy of more advanced esophageal cancers has also evolved with patients who only have evidence of regional lymph nodes undergoing esophagectomy, whereas those with more advanced disease are being treated with chemotherapy and radiation [3]. The technologies that have been developed to assist with detection and staging are still evolving, and their final implementation cannot be determined at this time; however, it is clear that gastroenterologists are entering a period of change in our clinical practice.

Chromoendoscopy for the detection of endoscopically “occult” cancers

One of the aims of esophageal cancer therapy has been to develop methods to image early esophageal cancers. This has already been accomplished to a large extent in squamous cell cancers of the esophagus with the development of chromoendoscopic techniques that use 1% Lugol solution. The iodine in the solution rapidly stains glycogen in normal squamous mucosa brown, and areas of dysplasia or early cancer are unstained [4]. One of the recent developments in the use of Lugol solution has been the finding that multiple areas of nonstaining squamous mucosa of patients with head and neck cancers may help predict the presence of synchronous esophageal cancers [5]. In this study of 389 Japanese patients, 14% were found to have synchronous squamous esophageal cancers. Of these patients, 55% had many irregular areas that did not stain with Lugol solution. However, one caveat to this study has been the very high incidence of squamous cell cancers of the esophagus in Japan and the ability to translate these findings to the United States. Certainly, though, patients who have had identified risk factors for squamous cell cancers such as alcohol and tobacco use who are found to have head and neck cancer may well have acquired a “field” defect in their esophageal mucosa that allows cancer formation in the squamous esophagus.

Chromoendoscopy for Barrett esophagus has also been studied in the past few years. This technique generally consists of using a vital dye, 0.5% methylene blue has been the choice of most investigators, which is applied to the surface of the esophagus after the mucous layer has been removed. The dye is generally thought to enhance detection of intestinal metaplasia, although areas of high-grade dysplasia may not stain. It was initially thought that methylene blue was only of value in detecting intestinal metaplasia in longer segments of Barrett esophagus [6]. A recent study using methylene blue dye in combination with magnifying endoscopy has been reported for the detection of short-segment Barrett esophagus. This study investigated 30 patients in Japan with a columnar segment less than 1 cm in length with 80% sensitivity for detecting intestinal metaplasia in stained areas and 96% specificity. However, the clinical impact of finding these short segments of Barrett esophagus is debatable given the low incidence of cancer in these patients unless dysplasia is found. Unfortunately, despite initial encouraging results, the most recent studies seem to indicate that the sensitivity of methylene blue for high-grade dysplasia was only 37% in a group of 35 patients who were screened [7].

Methylene blue has been long known to be a photosensitizer as well as a vital dye. The large molecule can absorb light and actually has been used to destroy cells, viruses, and bacteria *in vitro* by binding to both cell membranes and DNA [8]. One of the most intriguing investigations reported recently found that the white light from endoscopy light sources actually activates

methylene blue to produce a photodynamic effect [9]. This report actually found that methylene blue can produce oxidative damage to DNA of cells in Barrett mucosa when applied during endoscopy. This could potentially accelerate the carcinogenesis of Barrett esophagus when being used in a genetically unstable tissue.

Magnification endoscopy

Magnifying endoscopes have been available to identify mucosal abnormalities in the gastrointestinal tract for several years. Most commonly, they are used in combination with chromoendoscopy to visualize changes in the surface pattern to diagnose malignancy or dysplasia. This has recently been applied to examination of tumor vasculature in early squamous cell cancers in Japan to determine the depth of mucosal tumor invasion [10]. The vascular pattern was found to be distinctly different for tumors that were confined to the mucosa versus those that penetrated the submucosa. Tumor depth of invasion could be accurately predicted using the vascular appearance in 83% of 72 cases. Submucosal tumors had complete replacement of the vasculature with tumor vessels, whereas those with mucosal disease still had evidence of intrapapillary capillary loops. These findings correspond with our current understanding of early cancers that acquire invasion and angiogenesis factors as they penetrate the basement membrane into the submucosa.

Magnification endoscopy has also been used to detect intestinal metaplasia of the gastric cardia recently [11]. There were several different patterns noted, with the “ridged” pattern most closely associated with intestinal metaplasia in 96% of cases. However, the clinical significance of cardia intestinal metaplasia still remains to be determined.

Optical diagnosis of esophageal cancer

An important advance in the treatment of esophageal cancer would be the ability to determine the presence of malignancy during the endoscopic procedure. This includes the ability to detect visually occult disease as well as confirm the histologic diagnosis without the need for actually performing a biopsy. Technologies that have been developed to accomplish these goals include fluorescence spectroscopy, fluorescence imaging, light scattering spectroscopy, optical coherence tomography, and Raman spectroscopy. Most of these technologies have in common the interaction of light energy with specific molecules within the tissue that absorb some of energy, resulting in altered tissue spectra that have been found to be related to the tissue type. In the past 2 years, several studies have been performed that demonstrated the feasibility of these technologies in patients.

Detection of dysplasia within Barrett esophagus has been the goal of several studies because of the ease of access to the endoscopist and the difficulty in actually detecting lesions. Several recent studies have focused on the ability of agents to enhance the ability of fluorescence spectroscopy to detect dysplasia. Photodynamic therapy has employed agents that accumulate in neoplastic tissue. One of these agents that has primarily been used in Europe has been amino levulinic acid, which is taken into the cells and converted into protoporphyrin IX. This agent is fluorescent and was reported to enhance the detection of high-grade dysplasia in 20 patients with 77% sensitivity and 71% specificity using porphyrin fluorescence alone [12]. A larger study using amino levulinic acid and time-fated fluorescence in 53 patients found that there was significantly more normalized fluorescence in dysplastic tissue compared with nondysplastic [13]. However, the confidence intervals for these normalized values overlap to a large extent. In addition, another study found that amino levulinic acid used in 28 patients with Barrett esophagus was found in inflamed tissue, accounting for a third of the false positives in the study [14]. All these studies involved the use of a point spectroscopy device that is not easily applied to screening gastrointestinal mucosa.

Tissue autofluorescence has been used to detect dysplasia in Barrett esophagus by imaging the mucosa. This technique uses the fluorescence of endogenous fluorophores in the gastrointestinal mucosa to detect areas of dysplasia. An early version of this system was used in 35 patients with 21% sensitivity and 91% specificity for the detection of cancer or dysplasia versus nondysplastic Barrett mucosa [7].

Optical coherence tomography continues to advance in its imaging of the esophagus. This technology basically allows imaging at the histologic level by using light interference patterns similar to ultrasonography, which can create images by using sound waves. Initial reports established the potential of optical coherence tomography in identifying Barrett mucosa and dysplasia [15]. Recent studies have verified that optical coherence tomography can identify the muscularis mucosae accurately in *ex vivo* specimens and could identify high-grade dysplasia in 100% of cases with 95% sensitivity in a small series [16]. This imaging would allow careful delineation of the esophageal mucosa and greatly enhance the ability to enhance mucosa neoplasms. However, this technology is still very difficult to apply *in vivo* because of the long signal acquisition times and the limited depth of penetration. It is hoped that technological advances will enable the clinical application of this technique.

Endoscopic mucosal resection

Histologic examination is currently the gold standard of determination of cancer staging. Endoscopic mucosal resection allows the endoscopist to accurately determine the depth of tumor invasion because it is the only endoscopic technique that provides histology. This technology has been extensively studied in the past 2 years.

Studies from Japan where endoscopic mucosal resection has become the treatment of choice for superficial squamous cell cancer of the esophagus found that cancers confined to the superficial mucosa, m1 and m2, have virtually no chance of developing lymph node metastasis, regardless of the surface area involved [17]. However, cancers that penetrate the deep submucosa, sm2 and sm3, are quite likely to have metastasis. Cancers that are in the deep mucosa or superficial submucosa can have lymph node metastasis regardless of the size of the lesion, which appears to be enhanced if there is attachment or infiltration of the muscularis mucosa.

Endoscopic mucosal resection has also been used to treat Barrett esophagus by circumferentially removing the entire Barrett segment [18,19]. This technique has only been done in a small number of patients, but it does offer the promise of being able to totally characterize a Barrett segment with ablative therapy. The combination of photodynamic therapy and endoscopic mucosal resection has also been used to treat adenocarcinoma in Barrett esophagus [2]. The mucosal resection is used to determine the depth of penetration of the tumor similar to squamous cell cancers. Endoscopic ultrasonography (EUS) is also performed to assess the patient for the presence of regional lymph nodes.

Endoscopic ultrasonography

The use of EUS in the staging of esophageal cancer has been studied. The primary advantage of EUS has been the ability to accurately stage tumor invasion and regional lymph nodes. It also has the ability to confirm the results of imaging with cytology from fine needle aspiration. The primary limitation of EUS has been in the detection of distant metastasis in the liver or lungs. In a recent decision analysis model of the use of EUS in esophageal cancer that has not metastasized, EUS was thought to be a cost-effective next step for staging if celiac lymph node prevalence was greater than 16% [20]. A similar analysis assessing the cost-effectiveness of using multiple combinations of diagnostic strategies including positron emission tomography (PET), CT, EUS and fine needle aspirate, and laparoscopy [21]. This analysis found that the

combination of PET and EUS was the most cost-effective strategy in the evaluation of esophageal cancer. These analyses were performed for the typical esophageal cancer that is often metastatic. Interestingly, a study was reported that confirmed previous reports that endoscopy alone had the ability to stage advanced cancers. In one series of 209 patients, endoscopy was 89% accurate in determining tumor staging compared with surgical or EUS staging [22]. Patients with large bulky circumferential tumors who present with dysphagia are likely to have advanced disease and will require tests to confirm this. Patients who have cancers that are less than 2 cm in diameter and are asymptomatic are more likely to have early disease. In a new twist, the endoscopic appearance predicts the stage of the tumor as determined by EUS [23]. If a tumor created a luminal stenosis, it was at least a T3 and possibly a T4 tumor on EUS. Otherwise, tumor stage correlated well with the length of the tumor. Those tumors less than 5 cm in length were 92% likely to be a T2 or T1 lesion.

Computed axial tomography and positron emission tomography

The most commonly used staging procedure in esophageal cancer is computed axial tomography. The particular strength of this test is the ability to detect distant metastatic disease. It does not detect early stage cancer or advanced regional cancer with the sensitivity of EUS. The development of ultrasound miniproboscopes have higher resolution than the echoendoscopes and are more accurate than spiral CT (84% vs 68%) in defining early stage cancer [24]. In advanced stage disease, comparisons with EUS and fine needle aspiration indicate that CT is not as sensitive for detecting celiac lymph node disease or T4 carcinoma [25].

Positron emission tomography has also been gaining favor as a test for distant metastasis of esophageal cancer. The technology is based on the theory that tumors normally metabolize glucose at a faster rate than normal tissues. However, inflammatory tissues are also fast glucose metabolizers and can create false positives that can be problematic [26]. Recently, a study of 42 patients was reported that found that PET was only 37% sensitive for peritumoral lymph nodes versus 89% for EUS, although its specificity was greater at 100% versus 54% with EUS without fine needle aspiration [27]. False positives were found primarily in the jugular node region. False positives can also occur with PET in situations of low or diffuse tumor burden such as peritoneal carcinomatosis and celiac adenopathy. PET has been found to be more specific than CT in detecting abdominal or thoracic nodes, but CT had greater overall accuracy [28]. PET cannot define the tumor stage because it cannot resolve the layers of the esophagus. Because of these factors, PET will probably be used as the first staging tool for esophageal cancer.

Magnetic resonance imaging

MRI has not been used in any large series for determining tumor stage in esophageal cancer, and parameters probably have not been idealized. There was one reported study involving 86 patients who had MRI compared with other staging techniques [24]. These investigators found that MRI had a 40% sensitivity and 63% specificity in staging esophageal cancer. MRI might be thought to provide better information on tumor stage. However, in this study, the accuracy of MRI was only 60% in tumor staging.

Thoracoscopy and laparoscopy

Minimally invasive forms of surgical staging have been proposed to assist in accurately staging esophageal cancer because the open operation carries a high morbidity rate. One series that was reported recently assessed the results of 111 patients with esophageal cancer who were staged by CT, MRI, and EUS followed by laparoscopy and thoracoscopy [29]. These surgeons found that the primary areas that were not well studied with conventional staging techniques

were T4 tumors and mediastinal lymph nodes. They found that thoracoscopy and laparoscopy greatly added to the staging process. Of note, PET scans were not included in this study.

Conclusion

Staging of esophageal cancer has progressed significantly in recent years. Information from the initial diagnostic endoscopy can give the physician a great deal of information regarding the need for further staging studies. If the patient presents with dysphagia and has significant luminal narrowing, the patient undoubtedly has advanced stage cancer and possible metastatic disease. A strategy to document evidence of distant metastasis may be the most effective in this circumstance. This could be done using CT or PET depending on local availability. EUS with fine needle aspiration could be performed to establish histologic evidence of metastatic cancer. If the results are negative, additional staging could be performed with laparoscopy and thoracoscopy, if available. Conversely, if the patient has no dysphagia and has a relatively small tumor, then local staging studies could be EUS or endoscopic mucosal resection if the tumor is small enough. If the tumor were shown to be confined to the upper mucosa, the risk of metastasis is virtually none, and it could be argued that additional staging is not necessary. The tumor could be excised endoscopically, especially if it were a squamous cell tumor. The endoscopic treatment of superficial adenocarcinoma in Barrett esophagus has potential but requires validation. Overall, the future of esophageal cancer staging will be affected to a large extent by the development of new treatment methods and adaptation of guidelines for screening premalignant lesions.

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Abbreviations

EUS

endoscopic ultrasonography

PET

positron emission tomography