

Update on Endoscopy-Based Imaging Techniques in the Diagnosis of Esophageal Cancer

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ABSTRACT: The early diagnosis of esophageal cancer is necessary for improving the surviving of patients with this disease. To ensure an accurate staging, there are necessary imaging tests to establish the local and regional extension, as well as excluding the metastases. Computed tomography (CT), endoscopic ultrasonography (EUS), and positron emission computed tomography (PET-CT) constitute standard methods for esophageal cancer staging. These techniques are complementary; using only one of these tests is not suitable for correct staging. The role of EUS has improved the doctors' ability to evaluate and select the patients to undergo surgery, radiotherapy, or chemotherapy.

KEYWORDS: esophageal cancer, digestive endoscopy, medical imaging

Introduction

Esophageal cancer constitutes an extremely aggressive pathology, with unsatisfying long term results of the actual therapeutic methods, mainly because of the advanced stage at the time of diagnosis.

Despite progression of investigative means for early diagnosis of esophageal cancer, the percent of superficial cancers that undergo surgery is still under 10 from the total operated esophageal cancers [1].

In order to obtain the best therapeutic results a very accurate staging for esophageal cancer is mandatory. While for the positive diagnosis of esophageal cancer the upper digestive endoscopy with multiple biopsies is an absolute necessity, EUS, CT, and PET-CT are considered standard methods for esophageal cancer correct staging. Those diagnostic test are used in order to establish local, regional and distant extension. The imaging methods used for the correct and complete diagnosis of this disease are complementary; the use of a single method being considered insufficient and inadequate for a correct staging [2].

Upper digestive endoscopy confirms the macroscopic diagnosis, the topography of the lesion, and can take samples for histologic examination. Because of its propriety to distinguish the esophageal layers, EUS has an important role to establish the local tumoral extension. The actual performance regarding the diagnosis and especially the diagnosis of esophageal adenocarcinoma associated to Barrett esophagus has improved due to modern complementary imaging methods.

Due to grate variability regarding the type of diagnostic around the world (screening vs. non-screening, incidental vs. symptomatic), differences in technology or medical human resource development between different centers and, most of all, due to medical accessibility issues there is low standardization regarding the full diagnostic protocol of esophageal carcinomas and premalignant lesions. However, there are a few endoscopic or endoscopic-based techniques that proved their efficiency and entered current practice (we will refer them as *current standards*) while others, mostly highly specialized, still need validation and development, being referred here as *emerging/experimental technologies*.

Current standards

Upper digestive endoscopy or esophagogastroduodenoscopy (EGD)

EGD has a central role for diagnosis of esophageal cancer in patients who come to specialist for symptoms onset or incidentally, during investigation for other pathology. Also, EGD represents a screening method for esophageal cancer detection during Barrett esophagus evolution. EGD establishes the macroscopic diagnosis of esophageal cancer and contributes to histologic diagnosis by allowing biopsy samples from the lesions. In the search for better diagnostic capabilities a lot of improvements have been made to endoscopes in terms of thickness, length, “cold” light, distal light, optic amplifying and better insufflation/aspiration. Therapeutic means were specially developed for endoscopic use and there is a constant improvement of video capture devices attached to the endoscopes. The diagnostic performance has increased by association of emerging complementary methods such as: chromo-endoscopy, zoom in endoscopy, autofluorescence endoscopy with narrow band imaging, endoscopic confocal microscopy, endocytoscopy, tomography by optical coherence [3].

All those efforts of technical improvements were mainly made in order to allow an earlier diagnostic and/or lower the false negative rate of endoscopic examinations in esophageal cancers. The early stage esophageal cancer can have a great polymorphism and appear like small nodular zone, small ulceration, or just a color modification of the mucosa, reasons for which the examiner can miss the lesion. Advanced esophageal cancer appears exofitic with secondary stenosis (Fig.1), as ulceration (Fig.2), infiltrative, or as mixed forms. Japanese

society for esophageal diseases has elaborated a classification for esophageal cancer based on endoscopic appearance (Table 1) (by Kumagei) [4,5].



Fig.1. Exofitic (polypoid) esophageal carcinoma with secondary stenosis

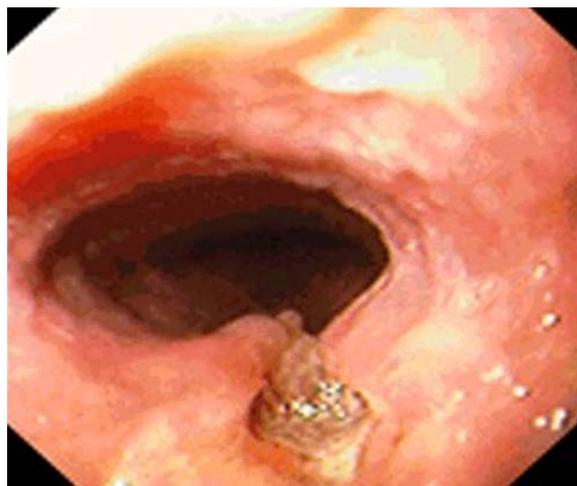


Fig.2. Ulcerative esophageal carcinoma

Table 1. Japanese macroscopic classification of esophageal cancer

I. Type 0-early esophageal cancer	1. Polypoid	
	2. Plane	a.elevated
		b.flat
		c.ulcerative
3. Erosive		
II. Advanced esophageal cancer	Type 1-Polypoid	
	Type 2-Ulcerative non-infiltrative	
	Type 3-Ulcerative infiltrative	
	Type 4-Diffuse infiltrative	
	Type 5-Non-classifiable/other	

Esophageal endoscopy does not distinguish between adenocarcinoma and squamous-cell carcinoma, but it offers information regarding

the topography of the tumor (also, it is known that the squamous carcinoma is often located on the upper segment of the esophagus, while the

adenocarcinomas are mostly located on the distal segment).

The accuracy of the diagnosis increases with the number of biopsy samples taken. In a study conducted on 202 patients with advanced esophageal cancer, the percent of correct diagnosis increased from 93% when only one sample was taken, to 98% when 7 samples were taken [4].

Known as premalignant lesion, the Barrett esophagus is periodically investigated by endoscopy to detect high grade dysplasia and esophageal adenocarcinoma. The Barrett's esophagus mucosa is biopsied from 2 to 2 centimeters, in every one of the 4th quadrants. Extra samples must be taken from every suspicious area (Seattle protocol) [5].

Modern techniques of endoscopic diagnosis have over 80% specificity, permitting a smaller number of biopsies. They are used especially for esophageal adenocarcinoma associated to Barrett esophagus [6].

Esophageal endoscopic ultrasonography

EUS represents the most accurate method to establish local and regional extension, with an accuracy to evaluate the tumor (T) of 85-90% and to evaluate the lymph nodes (N) (Fig.3) of 75% [7]. This method can associate fine needle biopsy (EUS-FNA) for the lymph nodes, or tissue samples taken using a TRU-CUT endoscopic biopsy system. The association between EUS and fine needle biopsy determine an increase with 20% of N1 stage detection from previous diagnosed N0 cases [8]. The possibility to evaluate T parameter (parietal invasion) (Fig.4) and to associate fine needle biopsy emphasizes the importance of this method [9].



Fig.3. EUS visualization of periesophageal adenopathies



Fig.4. EUS visualization of sm2 esophageal cancer after tumor localization using NBI mode

EUS is less accurate in detecting submucosal invasion (T1a versus T1b) for patients with high grade dysplasia and intramucosal cancer [10] and has a low and still unclear involvement in minimally invasive treatment of intramucosal cancers [11]. Despite all the above, EUS with fine needle biopsy can diagnose malignant lymph nodes invasion of early stage esophageal cancer and it can identify the patients that are not suitable for endoscopic treatment [12].

A difficult problem regarding esophageal cancer staging is encountered when the cancer is complicated with stenosis that cannot be passed with the endoscope. In these quite often encountered situations (in some series these cases represent over 70% from total) the solution can be the use of a thinner probe, of 6Ch, or performing esophageal dilatations [8]. However these cases are usually T3 or T4 and the use of dilatation is questionable for EUS purposes only, due to high risk of perforation or bleeding.

A review of 21 series of patients has emphasized that the accuracy of diagnosis is variable with T (tumor) stage. So, the accuracy for diagnosis for T1 cases has been 83.5%, with 16.5% over-staged tumors; the accuracy for T2 cases has been 73% with 10% over-staged tumors; the accuracy for T3 cases has been 89% with 5% over-staged tumors; the accuracy for T4 cases has been 89% with 11% under-staged tumors. A certain patient has 24 times more chances to be N1 when the EUS detected regional lymph nodes [12-14].

For a patient with poorly differentiated adenocarcinoma the chances for N1 stage are of 17% for T1 tumors, 55% for T2, 83% for T3, and 88% for T4. But a N0 EUS staging doesn't exclude and N1 pathology [12].

Concerning a recent retrospective study on 135 patients with high grade dysplasia or in situ carcinoma, EUS has not detected pathologic modifications of esophageal wall [3]. It becomes then obvious that the staging must be completed with other tests. Although there are multiple imaging methods for esophageal cancer staging, the appropriate imaging diagnostic sequence has not been yet defined. Schreus et al. have reserved EUS for those cases where the resection seems possible, saying that PET-CT is the most accurate predictive method as first used imaging method for staging [12].

Chromoendoscopy

It is a relative simple, easy to apply method, cheap and safe. It is based on applying stain on suspect esophageal mucosa using a catheter, during usual endoscopy [15].

- A series of staining agents are used, such as:
- Absorptive staining agents (Lugol solution, methylene blue, toluidine blue, violet crystal 0.5%);
 - Contrast agents (indigo carmine);

- Reactive agents (acetic acid 1.5-3%).

Cromoendoscopy using Lugol, the most used staining agent in Japan, has led to more frequently superficial esophageal cancer diagnosis. After the application of the Lugol solution, the neoplastic lesions constantly remain unstained, allowing an accurate biopsy. High grade dysplasia can also remain unstained or with altered pattern. However the method does not have the ability to distinguish between low grade dysplasia and non-dysplastic forms of Barret’s esophagus [16].

Magnification endoscopy

Magnification endoscopy and the usage of columnar epithelial instillations with various staining agents, has led to identifying some characteristic aspects specific for dysplastic lesions, and focused biopsy have improved the diagnostic rate for dysplasia and adenocarcinoma [17].

Inoue has described 5 types of patterns for squamous carcinoma, associated to a certain histologic stage (Table 2) [18].

Table 2. Classification of pattern changes encountered in the esophagus using magnification endoscopy (after Inoue’s classification of intra-papillary capillary loop in esophagus)

Type	Intrapapillary capillary lining (IPCL)	Lugol solution staining
I. Normal	Normal IPCL	Normal
II. Esophagitis	IPCL enlarging and elongation	Slightly stained
III. Low grade dysplasia	IPCL minimum modifications	Unstained
IV. High grade dysplasia	2 or 3 modifications of 4 possible	Unstained
V. Carcinoma	All 4 modifications: dilation, tortuous weaving, irregular caliber and form variation	Unstained

The diagnostic accuracy of magnification endoscopy to determine the depth of invasion is 98.8% for m1 and m2 and 69% for m3 [19].

Autofluorescence endoscopy

The technique is based on the fact that tissues can emit light due to some molecules named fluorophores, which emit fluorescent light when excited by ultraviolet light. Known fluorophores are porphyrins, collagen, flavins, amino-aromatic acids [20]. The changes in metabolism and structure of inflamed tissue, dysplastic cells or neoplastic ones, alter the light emitting pattern so the interested areas can be clearly distinguished from normal mucosa. Due to this behavior, the method allows the identification of areas of dysplasia, hence the possibility of taking focused biopsies. For populations with high prevalence for dysplasia, the method is superior when comparing to basic endoscopy with randomized biopsy [21]. Another method based on autofluorescence

principle is laser-induced fluorescence spectroscopy (LIFS), where the excitant is a high energy laser beam [6]. The dysplastic and neoplastic cells emit different wave-length light based on the fact that the rapport between nucleus and cytoplasm is higher for dysplastic and neoplastic cells.

Narrow band imaging (NBI)

It is based on the dependence between the light’s wave length and the depth of penetration. The depth of penetration is higher for higher wave length. Modern endoscopes can optically or electronically filter the light emitted by the light source in order to expose the tissues to the desired wave-length light. Based on the absorption and depth of penetration the examiner can clearly characterize the pit pattern and vasculature of suspect areas and take oriented biopsies.

The sensitivity of NBI for superficial squamous carcinoma is over 95% [22].

Emerging/experimental technologies

Confocal endomicroscopy and confocal fluorescence endomicroscopy

Technology evolution with chips, lens and mechanism miniaturizing allowed the translation of the microscope from the pathology lab in the tip of the endoscopes that explore the living patient. The method permits histologic unstained pictures of the esophageal mucosa taken for different depth in the tissue. The method is not a routine one since interpretation of the images needs ultra-specialization, there is lack of standardization and the costs are not neglectable. Two different systems were developed [23]. The association between Pentax and Optiscan placed a confocal endomicroscope in the tip of the endoscope using a single fiber and an optical window in contact with the tissues to examine. The depth of the image within the tissue is regulated using an electromagnetic mechanism between 0 to 250 μ m from the surface. The system called Optiscan/Pentax ISC-1000 was developed for colorectal evaluation but was also used in upper gastrointestinal tract [23]. The second system comes from Cellvizio as independent system with changeable miniprobes that can be used with standard endoscopes via working- channel. Numerous miniprobes were developed since every single miniprobe has a fixed confocal depth. Due to its versatility the system was largely used in different studies concerning early detection of metaplasia, high grade dysplasia or adenocarcinoma on Barrett's esophagus with proved specificity and sensibility over 96% [24]. Confocal fluorescence endomicroscopy uses as principle fluorescent excitation of the tissues, after exposal to laser light of low power with blue emission. After exposal, the reflected fluorescent radiation is detected, somehow obtaining histologic colored pictures that are comparable with images from ex-vivo fluorescence microscopy. This method allows a smaller number of biopsies, with sensitivity of 70% and specificity of 90% for adenocarcinoma diagnosis, but it still needs validation before taking it to current practice [25].

Endocytoscopy

It is also a still experimental method based on surface high magnification using optical lens applied directly on the in-vivo stained mucosa. It allows obtaining real time microscopic images of the mucosa [26]. The method can be used complementary in dysplasia and early (surface) neoplasia, especially in Barrett's esophagus.

Optical coherence tomography (OCT)

This method uses laser light obtaining a resolution of 10 microns. It is used for detecting high grade dysplasia in patients with Barrett esophagus [27]. The sensitivity of the method to determine m1 is 97%, and specificity is 92%; for patients with high grade dysplasia, the sensitivity of detecting m1 is 100% and specificity is 85% [28].

Conclusions

Endoscopic ultrasonography, computerized tomography, and positron emission tomography represent golden standard for diagnosis and staging of esophageal cancer. Esophageal endoscopy confirms macroscopic and histologic diagnosis of esophageal cancer, as well as tumor topography but can miss early cancer. Endoscopic ultrasonography is the most appropriate method that establishes the local and regional extension in esophageal cancer and it offers very important information useful to guide the therapeutic strategy. Endoscopic ultrasonography with fine needle biopsy defines more accurately esophageal cancer staging but a N0 endoscopic ultrasound evaluation should not exclude N1 pathology. Relatively new endoscopy-based techniques such NBI, chromoendoscopy, magnification endoscopy, autofluorescence endoscopy are currently used to detect early cancer especially in high risk patients. In patients with Barrettesophagus this methods can surprise the apparition of high grade dysplasia. Other new imaging endoscopic techniques such confocal endo-microscopy or optical coherence tomography proved their usefulness, but need further studies before entering current practice.

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