Review Article

Endoscopic Screening for Esophageal Squamous Cell Carcinoma

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Abstract

Esophageal cancer (EC) is the eighth common cancer and the sixth most common cause of death from cancer worldwide. Esophageal squamous cell carcinoma (ESCC) remains the most common type of EC in the developing world and an important health problem in high-risk areas. Most of ESCC cases present in late stages, resulting in delayed diagnosis and poor prognosis. Prevention is the most effective strategy to control ESCC. Primary and secondary preventive methods may be considered for ESCC. In primary prevention, we try to avoid known risk factors. The aim of the secondary preventive method (ESCC screening programs) is to detect and eliminate premalignant precursor lesion of ESCC, preventing its progression into advanced stages. Similar to all population-based screening programs, any screening for early detection of ESCC must be cost-effective; otherwise, screening may not be indicated in that population. Endoscopy with iodine staining has been accepted as a population-level ESCC screening program in some high-risk areas including parts of China. This method may be too expensive and invasive in other high-risk communities. Nonendoscopic methods may be more applicable in these populations for population-based screenings. The limitations (questionable validity and costs) of new endoscopic imaging modalities, including narrow-band imaging (NBI), made them inappropriate to be used in population-level ESCC screening programs. Low-cost, less-invasive endoscopic imaging methods with acceptable diagnostic performance may make screening of ESCC in high-risk areas cost-effective.

Keywords: Carcinoma, endoscopic screening, esophageal cancer, Iran, squamous cell carcinoma

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Epidemiology of esophageal cancer

Esophageal cancer (EC) is the eighth common cancer worldwide causing over 400,000 deaths in 2008.[1] It is responsible for about 5.4% of all cancer-related deaths and was reported as the sixth most common cause of death from cancer.[1] Considerable variations were reported for incidence of EC between different parts of the world. A geographic area extending from northern Iran to north-central China (Asian belt of EC) was considered as high- risk area for EC.[2–4] Areas with intermediate risk of EC include Southeast Africa and parts of South America.[3] Other parts of the world including the USA were reported as low-risk ones.[1] EC is more common in men and more than 80% of cases occur in developing countries.[1] Squamous cell carcinoma (SCC) and adenocarcinoma are the most common types of EC.[2,5] Reports in the 1960s suggested that the morphologic diagnosis in about 90% of EC cases were esophageal SCC (ESCC).[3] Although recent studies showed an increase in esophageal adenocarcinoma and a decrease in ESCC in the Western countries,[6–8] other reports from developing world including Iran suggested that ESCC still comprises more than 90% of EC cases.[9,10] So, ESCC remains the most common type of EC in the developing world and an important health problem in high-risk areas.[11]

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Pathogenesis and etiology of ESCC

ESCC typically occurs by progression from dysplastic lesions within the normal squamous epithelium of the esophagus (Figure 1).[3] Esophageal squamous dysplasia (ESD) has been suggested as the only clinically important premalignant precursor lesion for ESCC.[12,13] ESDs are classified into two groups. The first is low-grade dysplasia, which includes mild and moderate dysplasia. The second is high-grade dysplasia, which includes severe dysplasia.[3] Over months to years ESDs grow into tumor mass (ESCC).[14]

Various factors may increase the risk of ESCC.[15] These factors affect on the process of ESD development and its progression into ESCC. Genetic susceptibility was suggested to play a role in pathogenesis of ESCC.[16,17] Relationships between some environmental factors and the risk of ESCC were reported.[18,19] Patients' characteristics including alcohol drinking,[20] tobacco smoking,[20,21] opium consumption,[21] nass chewing,[21] hot tea consumption,[22] mate drinking,[23] low intake of fruits and vegetables,[24] low socioeconomic status,[25] and tooth loss[26] may play role in development of ESCC. So, ESCC is a complex and multifactorial disease.

Prognosis of ESCC

Esophageal wall does not have true serosal layer. This makes ESCC a progressive cancer with relatively rapid invasion into neighboring structures.[27] Most of ESCC cases present in late stages, resulting in delayed diagnosis of the disease. Consequently, prognosis is poor in these patients. The overall five-year survival of ESCC patients was reported as low as 9%.[14] But, if the disease is detected in early stages, the survival rates will be considerably improved. Results of a study on 230 EC cases suggested that the

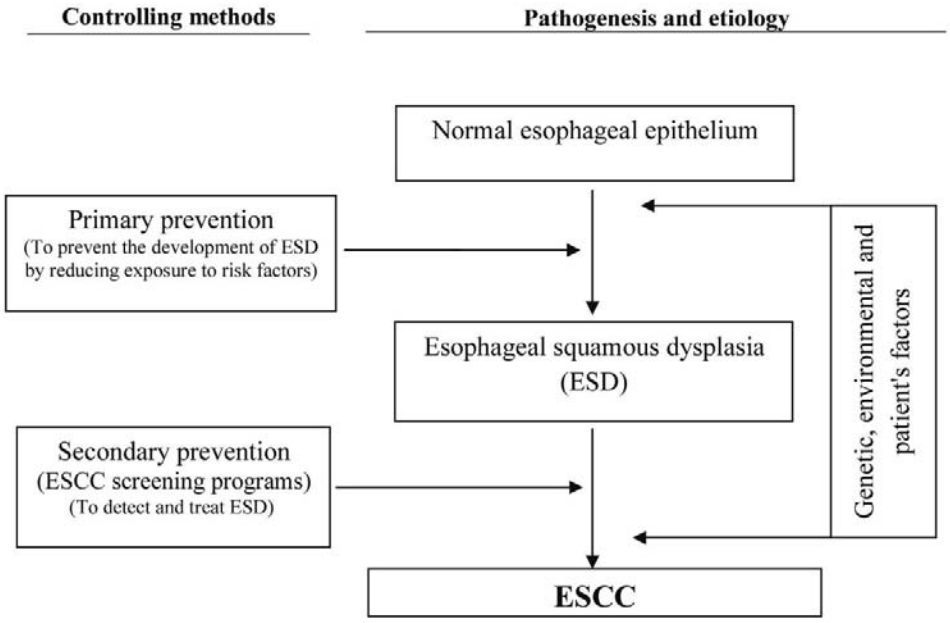

Figure 1. Pathogenesis, etiology, and controlling methods of esophageal squamous cell carcinoma (ESCC).

five-year survival rate in patients with mucosal cancer (84%) was higher than those with submucosal cancer (64%).[28] Wang, et al. reported five-year survival rates of 84.1% and 100% in early stages of EC cases with esophagectomy and endoscopic mucosectomy, respectively.[29] In another study from Japan, the five-year survival rates in EC with stages 0, I, and IIA-IVB were 83%, 47%, and 0%, respectively.[30] Generally, the survival rate of EC was higher in high-income countries[31,32] than low- and middle- income countries.[33,34]

Detecting ESCC in earlier stages will decrease the costs, incidence, mortality, and consequently the burden of the disease.[35] Liu, et al. and Yang J, et al. showed that detecting and treating EC patients in early stages will result in a considerable reduction in costs and increase in benefits.[36,37] Regarding the results of a study from Italy, lymph node metastasis did not occur in patients with lesions restricted to esophageal mucosa including ESDs and intraepithelial neoplasia (carcinoma *in situ*).[38] After invasion to submucosa, the rate of lymph node metastasis will increase dramatically. So, it is important to detect and control the disease in earlier stages. Detection and treatment of mucosal lesions will result in the best prognosis. Detecting these lesions should be considered as the main aim in early ESCC detection programs.

Controlling programs for ESCC

Appropriate treatment modality is usually selected for ESCC patients according to the stage of tumor.[3] Mucosal lesions including ESDs and carcinoma in situ are treated by endoscopic mucosal resection (EMR), while the therapeutic options in localized ESCC include surgical resection, radiotherapy, and chemotherapy.[3] Patients with advanced stage of ESCC may be treated by endoscopic palliative therapies such as laser therapy, argon plasma coagulation, esophageal dilation, and esophageal stent replacement.[3] Despite availability of a wide range of therapeutic options, prevention is the most effective strategy to control ESCC. Primary and secondary preventive methods may be considered for ESCC. In primary prevention, we try to prevent the initiation of the ESD (Figure 1). But ESD is a multifactorial condition and it may not be possible to identify and eliminate all of its risk factors. The aim of secondary prevention is to detect and eliminate ESD, preventing its progression into advanced stages. As mentioned earlier, the therapeutic options and prognosis of mucosal ESCC (carcinoma in situ) is the same as high-grade ESD. Therefore, carcinoma in situ of the esophagus may also be considered as an appropriate target in secondary prevention of ESCC. Endoscopic therapeutic options including EMR result in complete elimination of these mucosal lesions and give a normal life with high quality to the patients.[39]

Screening methods for ESCC

A screening method might have potential benefit for a disease if the following assumptions are true about it. Firstly, the disease in all or most of cases starts from a detectable preclinical phase. Secondly, in the absence of intervention, most or all cases in preclinical phase progress into clinical one.[40] In case of ESCC, both of the above- mentioned assumptions are true.[14] So, screening programs can be efficient and helpful for controlling ESCC. Secondary prevention (to detect ESD and carcinoma in situ) has been considered as basic design in screening programs of ESCC. Endoscopy is the diagnostic choice for esophageal mucosal lesions.[3,41] But it is an invasive and expensive method and especially is not accepted by asymptomatic cases.[42] Therefore, investigators tried to find a nonendoscopic screening method by considering a combination of various modalities such as cytologic examination and existence of various risk factors and molecular markers.[43] Despite the large number of studies conducted throughout the world, no method has yet been approved as an efficient nonendoscopic ESCC screening test,[3,44] and endoscopy remains as the best option for ESCC screening programs. A large number of studies have been conducted to develop the best endoscopic method for ESCC screening. We will

discuss about the details and results of these studies in the following section of this paper.

Endoscopy with iodine staining

The first and most important step of ESCC screening programs is to detect its premalignant lesions (ESD) as well as early-stage malignant lesions (carcinoma in situ). Endoscopy is considered as the method of choice for detecting these lesions and taking biopsy for histologic confirmation. However, these lesions are generally invisible during conventional white-light endoscopic examination of esophageal lumen. So, investigators tried to find a method to make mucosal lesions visible through endoscopic examination. Schiller for the first time introduced a method to highlight premalignant lesions (squamous dysplasia) of the cervix. They considered iodine staining for early detection of mucosal abnormalities of the cervix.[45] As epithelial cells of the cervix and esophagus are both of squamous cell type, a similar staining technique has been applied since the late 1960s to detect mucosal lesions of the esophagus.[46–49]

The superficial epithelium of the normal squamous epithelia (e.g., in the esophagus and cervix) contains abundant glycogen. Basically, iodine stains glycogen brown.[50,51] So, if normal esophageal epithelium is exposed to iodine, its color changes into dark brown. The glycogen content in abnormal mucosal lesion including squamous dysplasia and carcinoma in situ is very low, and the areas with those lesions remain unstained, so called as unstained lesion in endoscopic examination.[52,53]

Endoscopy with iodine (Lugol's solution) staining of the esophageal mucosa, so called as chromoendoscopy, has been used to detect esophageal mucosal lesions and suggested to be considered in ESCC early detection (screening) programs in different populations. Mandard, et al. used iodine staining in 37 esophageal specimens. They found normal esophageal mucosa as iodine-positive and invasive carcinoma and dysplastic lesions as iodine-negative zones. They finally suggested iodine staining for early endoscopic diagnosis of EC.[54] The usefulness of iodine staining to improve early detection of esophageal squamous neoplasia was reported by some investigators.[55–63]

These studies were conducted on different high- risk populations. The results of a study from Brazil on patients with head and neck cancer, showed that Lugol chromoendoscopy diagnosed 100% of high-grade intraepithelial neoplasia while the detection rate by standard endoscopy was 55%.[64] The results of other studies in similar high-risk populations also approved the validity of endoscopy with iodine staining as an effective ESCC screening method in patients with head and neck cancers.[65–69]

Yokoyama, et al.[70] conducted a screening program for early detection of EC on a cohort of 629 high- risk individuals in Japan (alcoholic males) and concluded that chromoendoscopy is a useful method to detect dysplastic and neoplastic lesions of the esophagus. Ban, et al. similarly showed the usefulness of endoscopy with iodine staining to detect early stages of EC in alcoholics.[71] In a study from Brazil, Lugol chromoendoscopy was used to detect ESD in 190 high-risk asymptomatic males (those who consumed alcohol, cigarette, and mate) and ESDs were successfully detected.[72] In a study on 225 healthy adults from a high EC-risk area in China, Dawsey, et al. found an increase, from 62% (before iodine staining) to 96% (after staining), in sensitivity of endoscopic examination for identifying high- grade ESD or ESCC.[41] The results showed that 55% of moderate ESD and 23% of severe ESD were detected only after staining.

Chromoendoscopy was also reported to be useful in assessing the characteristics of esophageal mucosal lesions. It was reported to be effective in identifying margin lines of the lesions.[73] Mori, et al. found that the thickness of the glycogen-containing cell layer was well identified by staining intensity. Their results showed that Lugol test can be used for precise delineation of borders of the lesions.[50] Kuwano, et al. similarly suggested endoscopic examination with Lugol staining as useful method to identify borders of early stages of EC.[74] Dawsey, et al. also found a positive relationship between size of unstained lesions and histologic diagnosis of the lesions (high-grade ESD or ESCC). They reported that the border of lesions in 88% of high-grade ESD and ESCC lesions were more clearly defined.[41]

Because of the above benefits and its high sensitivity and specificity, chromoendoscopy has been considered as the gold standard method for diagnosis of abnormal esophageal mucosal lesions in different research projects.[42,75] However, because of some limitations, it may not be accepted at population level in some high-risk regions including northeastern Iran. The first limitation is that endoscopy is an invasive procedure. Its costs may be relatively high, especially in low-resources communities. In addition, the Lugol's solution may cause complications including retrosternal pain and discomfort and even erosions or ulcers in the esophagus (due to mucosal irritation).[76]

There is also another important limitation for this technique. The results of some studies suggested that the specificity of chromoendoscopy for detecting ESD and early stages of ESCC was low. So, some investigators tried to find applicable methods to improve its specificity. Ishihara, et al. considered the pattern of color change after iodine staining for this reason.[77] After using Logol's solution during endoscopic examination, the neoplastic lesions of the esophagus initially change into whitish yellow color and then pink two to three minutes later. This pattern is called as pink sign in chromoendoscopy. Using this sign, Ishihara, et al. reported an acceptable accuracy (sensitivity = 88% and specificity = 95%) for chromoendoscopy to detect early stages of esophageal neoplasias. Further studies are warranted to determine if this technique is applicable for other high-risk areas. Anyway, modifying the standard chromoendoscopy may be helpful to develop a more applicable screening program for ESCC. Overall, considering chromoendoscopy for developing ESCC screening program should be individualized for each community. When cost-effectiveness and adherence of people, despite invasiveness of the procedure, are acceptable, chromoendoscopy may be used for population- level screening. Otherwise, nonendoscopic screening programs may be considered.[44]

Endoscopic tissue imaging without staining

Here we briefly review some recently developed endoscopic imaging modalities that do not use staining. However, the validity of almost all of these methods in detecting ESD and early-stage ESCC is under question and needs further investigation. These methods are generally expensive and are not available in many populations, in particular low-resources countries in which most of high ESCC-risk areas are located.[1] Therefore, these methods do not seem to be suitable for population-level screening programs in these populations.

Narrow-band imaging (NBI)

In NBI method, narrow-bandwidth filters in a red-green-blue se-

quential illumination system is used to enhance the accuracy of diagnosis.[78] As a result, contrast between the epithelial surface and the vascular pattern is increased and different images will be produced at various levels of the mucosa, resulting in similar contrast enhancement when compared to Lugol chromoendoscopy.[79] Adding NBI to standard endoscopy was helpful in early detection of ESCC.[80] Improvement in visualization of the intrapapillary capillary loops was the main advantage of this technique.[80] Different investigators reported high sensitivity and specificity for NBI to detect neoplastic lesions in esophageal mucosa.[81–83] Muto, et al. reported a sensitivity of 97.2% and a specificity of 88.9% for NBI system to detect secondary superficial ESCC lesions in patients with head and neck cancer. They suggested NBI as the standard method for screening ESCC in this high-risk population.[84]

Different findings may be detected in esophageal mucosa during NBI examination. The diagnostic values of these findings are not the same. The significance of different NBI findings was assessed by Ishihara, et al. They found that brownish epithelium and brownish dots are the most important NBI findings to be used for diagnosis of high-grade squamous neoplasia of the esophagus.[85] This finding needs to be investigated in larger multicenter studies to determine if it is applicable at population levels. There is another limitation for using NBI in primary care setting. Experience of endoscopist is an important issue for achieving successful results in NBI method. The results of a study from Japan showed that the sensitivity of NBI for detecting high-grade squamous neoplasia of the esophagus was significantly higher in experienced endoscopist (100%) than less experienced endoscopist (69%).[86]

The benefit of a combination of NBI system and magnifying endoscopy has been assessed in some studies. Yoshida, et al. reported more accurate assessment of esophageal lesions by considering such combination.[87] Goda, et al.[88] and Kawahara, et al.[89] also suggested that magnifying NBI endoscopy may be helpful for detecting and diagnosing superficial ESCC.

Confocal microscopy

In this method, the standard endoscope is combined with microscope image-processing unit. Adding fluorescent agents (acriflavine hydrochloride or fluorescein sodium) will provide cellular and histologic details of the tissue, resulting in detection of mucosal lesions.[90] Liu, et al. used confocal laser endomicroscopy (CLE) to detect superficial ESCC. They found that CLE can successfully distinguish cancerous from normal epithelium and suggested it as a potential good method for early detection of EC.[91] The potential problem with this system is the difficulty in obtaining good images. Further studies are needed to improve the validity of this method to detect mucosal lesions.

Endocytoscopy

This method makes it possible to observe the cellular nuclei in the GI tract in vivo. Endocytoscoy system has been used to assess the characteristics of cells on the surface layer of early stages of ECs.[92] By using this method it was possible to observe detailed histologic changes in esophageal lesions.[93] Fujishiro, et al. reported significant difference in characteristics of esophageal epithelial cells between cancerous and normal areas.[94] They found close correlation between endocytoscopic images and histologic finding of the esophageal biopsies. Evidences of neoplastic changes including, increased cell density and nuclear abnormalities were reported in 84% of biopsy samples from ESCC cases.[95]

Fluorescence endoscopy

In this method, real-time fluorescence images are provided by adding fluorescence agent to standard endoscope using image-processing module.[90] Polglase, et al. successfully used a fluorescence confocal endomicroscope to assess GI tract. They showed that this new method may be considered to visualize the cellular and subcellular structures of squamous epithelium of the esophagus and may be helpful to assess abnormal epithelial lesions of the esophagus.[96] Uedo, et al. used a videoendoscopy system with autofluorescence and reflectance for early detection of ECs. They could find 100% of superficial ECs using this method and reported that their method had an advantage over standard videoendoscopy.[97] However, the accuracy of this method in another study, was less than chromoendoscopy and NBI.[98]

Trimodal imaging

This technique consists of a combination of white-light endoscopy, autofluorescence and NBI. Some studies reported that this method may improve the detection of Barrett's dysplasia compared with standard endoscopy.[99–101] It may be considered for early detection of ESCC premalignant and malignant lesion. Future studies are needed to assess validity of this technique to detect ESDs and early stages of ESCC.

Optical coherence tomography

In this method, low-coherence infrared light is used to produce a high-resolution image of the epithelium.[90] It was used to diagnosis Barrett's dysplasia in the esophagus.[102] But its sensitivity was too low to be used in clinical setting.[103] Further studies are warranted to assess the validity of this method to detect esophageal squamous lesions.

Elastic scattering spectroscopy

This procedure is based on measurement of the epithelial elastic scattering index. This index may change as a result of alterations in cellular components (including nucleus and mitochondria) during neoplastic process. It is measured by inserting an optical probe through the instrument channel of the endoscope. A high sensitivity was reported for this technique to detect dysplasia and neoplasia in Barrett's esophagus.[104] Future studies are needed to determine if this method is also helpful for early detection of ESCC.

Conclusion

Designing endoscopic ESCC screening program should be individualized for each population. Similar to all population-based screening programs, any screening for early detection of ESCC must be cost-effective; otherwise, screening may not be indicated in that population. Endoscopy with iodine staining has been accepted as a population-level ESCC screening program in some high-risk areas including parts of China. This method may be too expensive and invasive in other high-risk communities. Nonendoscopic methods may be more applicable in these populations for population-based screenings. The limitations (questionable validity and costs) of new endoscopic imaging modalities, including NBI, made them inappropriate to be used in population-level ESCC screening programs. Low-cost, less-invasive endoscopic imaging methods with acceptable diagnostic performance may make screening of ESCC in high-risk areas cost-effective.

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